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Editorial

The World Journal of Biological Psychiatry – Past, Present and Future

The World Journal of Biological Psychiatry, the official journal of the World Federation of Societies of Biological Psychiatry (WFSBP), is now in its fourth year after its launch in January 2000. This encourages us to have a short glance back over the last three years and to think of new tasks for the future and progress that has to be made by the Journal.

Thanks to a generous unrestricted educational grant from Janssen-Cilag the Journal was able to develop on its own without the involvement of any sponsor in its scientific content. A major advantage of the Journal in comparison to other scientific journals is its worldwide distribution as it is sent to all members of national societies of biological psychiatry that are part of the WFSBP. As such the Journal is not only restricted to the Western hemisphere but also reaches Asia, Africa, South America and Australasia, thus doing full justice to its name.

The characteristics of the Journal as a true "World Journal" are also reflected by the countries of origin of scientists who have submitted their work to The World Journal of Biological Psychiatry. In the last three years papers from Europe, Africa, North and South America, Australia, Asia, etc., have appeared in the Journal. The broad geographic representation of authors allows this journal to provide readers in a unique way with the way of thinking of different cultures and countries on important issues of psychiatry.

The choice of different sections within the Journal appears to be a great success. In addition to reviews, original research papers and case reports, the Journal offers two rather novel categories of papers that have been widely accepted by authors. In the section "Summary of Original Research", authors may delineate their previous work and underline the main statements of their research, even if their original data have previously been published elsewhere. This gives the reader a comprehensive review of the original work of distinct research groups and also renders a new upcoming journal attractive for internationally well-known research groups to present their work. The section "Viewpoints" allows authors to make more subjective statements on various issues of biological psychiatry that even need not reflect the generally accepted way of thinking. Viewpoints represent more the thoughts of the authors than those of the Editorial Board or the WFSBP. Together with Case Reports and the publication of guidelines for the treatment of various psychiatric disorders, formulated by task forces founded by the WFSBP, The World Journal of Biological Psychiatry is on its way to becoming a leading publication medium that fosters new ways of thinking and interactive discussion among all continents.

Three years after the launch of the Journal it is also time to thank a lot of people who helped the Editorial Board to get the Journal flying. Very important tasks were accomplished by the WFSBP Administrative Office in Glasgow, Scotland, which is run by Gill Moore with the assistance of Euan Woodward, and by the Editorial Assistant in Munich, Jacqueline Klesing. With their aid it was possible to establish an internationally accepted review system and to provide reasonably short publication times after submission of work to the Journal, provided the work is accepted. It is also time to thank all the reviewers and members of the Editorial Board who helped to evaluate manuscripts and to support editorial decisions in an important way. Moreover, the important contributions of major research groups and of opinion leaders in the field of biological psychiatry has to be acknowledged as this greatly helped to get the Journal started. The Journal is proud of reviews of senior scientists and research groups that would have easily been accepted by other, well-established biomedical research journals. All the efforts of authors, reviewers, editorial offices and the Editorial Board were honoured by the acceptance of The World Journal of Biological Psychiatry for indexing in *Index Medicus* and MEDLINE in 2002, which was the earliest possible date for indexing. This was a great step forward for the Journal as it will now be more visible via the various databases, and will be even more attractive as a publication medium for future authors. All papers that were published in the first three volumes of the Journal will also be indexed, which is a further acknowledgement of the work of those who contributed to the development of the Journal in its early phase.

Putative future tasks – a glimpse into the future

What are the future challenges for The World Journal of Biological Psychiatry? Of course, it will be important to maintain the quality and timeliness of publication of the Journal, as well as the broad distribution and global authorship. In future, it will continuously be necessary to attract high quality original research papers. This is one of the reasons why the successful indexing of the Journal

is such an important step. Further tasks will be to develop an online reviewing system, as has been introduced by other major neuropsychiatric journals. Finally, The World Journal of Biological Psychiatry should be made available online to members of the WFSBP. These steps will further increase the availability of the Journal and speed up the timeliness of publication. With the successful indexing by MEDLINE, however, the Journal has entered the field of innovative, successful international journals and has to find its place in this competitive field. It is therefore important that the Journal is accepted for indexing by the Institute for Scientific Information (ISI) in order to obtain an impact factor, a citation half-life, etc., and thereby to find an appropriate place in the ranking of journals. For this purpose, it is extremely important that the Journal is guided by an Editorial Board whose members are highly respected scientists with appropriate personal citation indexes. This provides a basis for the attraction of future authors to submit work to the Journal which likely qualifies for a high citation rate within the scientific community. Besides the necessity of maintaining or even increasing the quality in order to be competitive in the international field, however, The World Journal also has to stick to its original dedication to be a real "World" Journal of Biological Psychiatry by further fostering and strengthening the scientific and educational dialogue in the field of biological psychiatry all over the world.

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Cigarette-Derived Nicotine is not a Medicine

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Summary

Regular smokers feel better when smoking than not smoking, and empirical studies confirm that nicotine reinstatement relieves feelings of stress, depression and anger. These acute mood changes have led to the belief that cigarette-derived nicotine can provide medicinal benefits for smokers. However, prospective studies of adolescents who take up cigarette smoking find that they report increased levels of anxiety, stress and depression. Furthermore, adults who quit smoking report enduring mood improvements. Thus the prospective data shows that the nicotine derived from cigarettes leads to heightened distress. The empirical patterns of mood change reported by regular smokers show why nicotine dependency is psychologically damaging. Regular smokers report average moods when replete with nicotine, but suffer mood deteriorations in-between cigarettes. Thus the supposed mood gains of smoking only represent the temporary relief of withdrawal symptoms. This mood relief becomes conditioned with smoke inhalation, which is why cigarettes are regarded positively by smokers. However, the repetitive experience of irritability and other abstinence symptoms in between cigarettes paradoxically causes smokers to suffer worse daily moods than non-smokers. The stronger the nicotine dependency the greater the mood decrements, helping to explain why disadvantaged individuals often smoke heavily and find quitting difficult. In conclusion, there is no empirical evidence that cigarettes provide medicinal benefits, but extensive data showing that nicotine dependency heightens psychological distress in tobacco smokers.

Key words: smoking, nicotine, dependency, stress, depression.

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The self-medication model for cigarette-derived nicotine

"The notion of self-medication is one of the most intuitively appealing theories about drug abuse. According to this hypothesis, drug abuse begins as a partially successful attempt to assuage painful feelings" (Glass 1990). The self-medication model for tobacco smoking is based upon two core findings. The first is that smokers feel better when smoking than when abstaining. They report feeling more relaxed, that smoking 'calms me down', increases pleasure, reduces anger, improves concentration, generates feelings of relief and increases contentment (Ikard et al. 1969; Russell et al. 1974). Furthermore the longer they go without a cigarette, the worse they feel, and the stronger the feelings of relief and satisfaction when they do smoke (Fant 1995). Hence many regular smokers come to believe that they need nicotine in order to cope with the stresses and strains of everyday life. Empirical studies confirm that regular smokers perform cognitive tasks far better when replete with nicotine than when abstaining (Parrott 1998; Perkins 1999; Revell 1988; Wesnes and Warburton 1983). This has led to the suggestion that nicotine can provide a range of psychological benefits (Gilbert 1995; Hughes 2000; Warburton 1992).

The second factor underlying the self-medication model is that rates of smoking tend to be high in many disadvantaged groups. Amongst those with a clinical diagnosis of depression, the proportion of smokers is high, cigarette consumption rates tend to be heavy, abstinence symptoms are severe and rates of quitting are low (Breslau et al. 1998; Glass 1990; Glassman et al. 1990; Hall et al. 1993; Kendler et al. 1993). These factors have led to the suggestion that depressed individuals may be using nicotine as a self-medication: "At the core of this causal explanation is the notion of self-medication, that smokers use nicotine to medicate their depressed mood" (Breslau et al. 1998, p161; Anda et al. 1999; Glass, 1990; Glassman et al. 1990; Hall et al. 1993; Kendler et al. 1993). Similar proposals have been debated for many other disadvantaged groups where smoking rates are high: anxiety/neurosis, schizophrenia, behavioural problems and attention deficit disorder (Gilbert 1995; Lambert and Hartsough 1998; Lynsky and Ferguson 1995; Piasecki and Newhouse 2000). There are, however, two alternative explanations for the high rates of

smoking amongst disadvantaged groups. They may be due to common association with a third superordinate factor, such as socio-economic deprivation (Glass 1990; Glassman et al. 1990; Hall et al. 1993; Kendler et al. 1993). The third possible explanation is that smoking directly causes psychological distress, although this is generally seen as the least likely explanation due to the absence of any explanatory model for how cigarette smoking might cause distress (Glassman et al. 1990; Hall et al. 1993; Kendler et al. 1993). For instance Glass (1990) noted: "The possibility that smoking leads to depression is not ruled out by these studies... but seems less plausible".

These three models have very different predictions for two key periods of smoking: initiation and cessation. The self-medication model states that medicinal benefits should be apparent in those who start using tobacco; adolescents who take-up smoking should report psychobiological gains, such as reduced stress and depression. In contrast, if smoking causes distress then novice smokers should suffer psychobiological impairments, such as increased levels of stress and depression. Whereas if the two factors are independent, then the initiation of smoking will not affect psychological functioning. Turning to smoking cessation, the self-medication model predicts that quitting will lead to psychobiological losses; that former smokers will become more anxious and depressed without their 'medicinal' nicotine. Whereas if these factors are unrelated, then cessation will leave psychobiological functioning unchanged. However if smoking is causing problems, then cessation will lead to psychobiological gains. The next two sections review the empirical evidence on psychobiological functions during these two key periods.

Smoking initiation: effects upon stress and depression

Cross-sectional surveys report a wide variety of psychobiological problems in adolescent smokers: increased stress, greater depression, decreased self-esteem, low self-efficacy and various other problems (Gilbert 1995; Lloyd and Lucas 1997; Mitic et al. 1985; Surgeon General 1988). The main limitation with cross-sectional evidence is that the different groups may come from different populations. Smokers and non-smokers may differ in constitutional characteristics, personality dimensions, socio-economic profiles or environmental stressors. The clearest evidence concerning the psychobiological consequences of smoking therefore comes from the following prospective/longitudinal studies.

Johnson et al. (2000) investigated the longitudinal association between cigarette use and anxiety disorders during adolescence and early adulthood. Heavy smoking around 16 years of

age led to an increase in generalized anxiety, agoraphobia and panic disorders five years later. In contrast, high anxiety while aged 16 did not lead to an increased incidence of later smoking. McGhee et al. (2000) monitored mental health, behavioural problems and drug use over several years in a group of New Zealand youngsters. Early socio-economic disadvantage led to an increased likelihood of taking up smoking when older. But those adolescents who became regular smokers reported an increase in psychobiological problems three years later: "Smoking at age 18 elevated the risk of anxiety/depressive disorder" (McGhee et al. 2000). Other prospective studies have shown a close association between the uptake of smoking, and increased levels of stress over time (Wills 1986). Similar findings have emerged in prospective studies of depression. Wu and Anthony (1999) prospectively investigated the temporal relationship between smoking initiation and depression in 8- to 14-year-old schoolchildren. They found that: "Smoking signalled a modestly increased risk for the subsequent onset of depressed mood" (Wu and Anthony 1999, p1837), whereas depressed mood at baseline did not increase the risk of later smoking. Patton et al. (1998) prospectively found that the uptake of smoking led to an increase in later depression. Breslau et al. (1998) undertook a five-year longitudinal study of young adults, and found that daily smoking at baseline led to significantly higher rates of later depression; high levels of depression at baseline also led to an increased incidence of later smoking. Goodman and Capitman (2000) confirmed that depressive symptoms and cigarette smoking during adolescence were closely interrelated. Cigarette use at baseline was a 'powerful determinant' for high depressive symptoms one year later; this was confirmed in every statistical model. The effects of depressive symptoms at baseline upon later smoking were more complicated. An initial bivariate analysis showed that pre-smoking depressive symptoms predicted the later uptake of smoking. But in the multivariate models, the predictive power of depressive symptoms was reduced as factors such as 'experimentation with cigarettes' became more important (Goodman and Capitman 2000).

Another variant of the self-medication model is that smoking/nicotine is used to alleviate the effects of distressing life events. This was investigated by Anda et al. (1999), who retrospectively assessed the effects of adverse childhood experiences upon depression and smoking in adulthood. Those individuals who had suffered more adverse childhood experiences, were more likely to be depressed as adults. But when smokers and non-smokers were analysed separately: "For any given number of adverse childhood experiences, current smokers were always more likely to have problems with depression" (Anda et al. 1999, p1657). Cigarette

smoking therefore did not mitigate the effects of childhood distress, but instead led to *increased* depression. Furthermore this increase occurred in all groups whether disadvantaged or not. Nicotine/smoking thus comprised an additional source of psychobiological distress, irrespective of experiential background (Parrott 2000b). In conclusion, the empirical evidence on smoking initiation provides no support for the self-medication model. No prospective study has found that the uptake of smoking leads to psychobiological gains. Instead they show the opposite, with smoking leading to increased levels of stress and depression. Disadvantaged adolescents also have an enhanced risk for becoming smokers, and thus of developing smoking-induced problems. The reason for this link between cigarette smoking and distress is explored later.

Smoking cessation: effects upon stress and depression

The US Surgeon General (1990) undertook an extensive review of cross-sectional studies comparing psychobiological functioning in former smokers and continuing smokers. Some studies found no differences between groups, others found that former smokers were significantly less stressed, but none found former smokers to be more stressed than continuing smokers. Similar conclusions were offered for depression, anger and self-esteem; either there were no differences between groups, or the former smokers displayed significantly better psychological functioning than continuing smokers (Surgeon General 1990, pp533-541). As noted earlier, there are inherent limitations in all cross-sectional data; thus the clearest evidence concerning the psychobiological effects of quitting comes from longitudinal studies.

Hughes (1992) prospectively assessed a battery of mood self-ratings for nine months before and after quitting. Increased levels of anger, restlessness and anxiety were found immediately after quitting; but over subsequent weeks and months, the whole spectrum of mood states improved over those found at baseline. Several prospective investigations have focused upon self-rated feelings of stress. Cohen and Lichtenstein (1990) assessed smokers at pre-cessation baseline, then one, three and six months afterwards. Those who failed to quit reported similar levels of high stress at each time point, whereas those who successfully stopped reported reduced levels of stress as time progressed. Initial stress levels at baseline were similar for both groups, thus it was not just the less stressed individuals who managed to quit. Carey et al. (1993) found that six months of total cessation led to significant reductions in self-rated feelings of stress. West and Hajek (1997) noted a significant reduction in self-rated anxiety following just a few weeks of cessation. Parrott (1995) found significantly reduced levels of self-rated stress after

three and six months of total abstinence; pre-cessation stress levels were similar in those who quit and those who failed, while stressful life events remained unchanged over the six month period. Thus cessation led to a true reduction in propensity for stress, unrelated to any environmental stressors. Chassin et al. (In Press) found decreased levels of stress in successful quitters six years after their previous assessment, when they had been actively smoking and reporting significantly higher levels of stress than non-smokers. Following the extended period of cessation, the stress levels for the former smokers reduced to those reported by non-smokers.

However, not every report has described psychological gains after quitting. Glassman et al. (1990) commented that clinically depressed smokers found quitting very difficult since they suffered from a marked increase in depressive symptoms, which generally led to the resumption of smoking. The immediate nicotine withdrawal syndrome can indeed be very severe, particularly in those with strong dependency. There is thus a need for longer-term prospective studies of heavily depressed/dependent quitting smokers (e.g. two years or more). The withdrawal syndrome is likely to be very severe and prolonged, but if abstinence can be maintained over this difficult period then mood gains should occur in the long-term. Some methods to facilitate cessation in depressed smokers are described later. Gilbert et al. (1998) reported mood decrements after quitting, but their study suffered from two crucial limitations. Firstly, moods were assessed for only four weeks and thus only covered the immediate withdrawal period, when adverse moods are expected. Secondly, participants were allowed an occasional cigarette while still being categorized as a 'quitter'. But heightened stress will occur in any smoker who continues to have the occasional cigarette, since they are effectively in a state of continuing severe withdrawal. Mood gains should only be expected in those who stop completely (Parrott 1999, 2000c). To summarize, regular smokers generally suffer adverse moods during the initial days and weeks after quitting. The longer-term effects are, however, beneficial, with significant mood gains after three to six months of continuous abstinence which endure for many years.

Nicotine dependency in cigarette smokers causes psychological distress

Although prospective studies have found that smoking leads to worse psychobiological functioning, they have generally failed to offer a clear explanation. Goodman and Capitman (2000) noted: "Available studies offer neither an empirical nor conceptual basis for the relationship between... smoking and symptoms of depression". McGhee et al. (2000) were unclear as to why adolescent smoking should lead to greater

stress and depression: 'The mechanism underlying this association remains unclear'. Glass (1990) thought that failed cessation attempts might lead to adverse moods in some smokers. Wu and Anthony (1999) suggested that nicotine or other components of tobacco smoke may alter depressive feelings via: "...central nervous system processes or thyroid function". Others have suggested that breathing difficulties may contribute to the increased rates of panic attack in smokers. There is, however, a very simple explanation for how cigarette smoking can cause distress: nicotine dependency. Regular smokers need nicotine to remain feeling normal, and suffer from adverse moods without it (Parrott 1994). It is the repetitive experience of adverse feelings in-between cigarettes which causes the smoker to suffer worse daily moods (Parrott 1995, 1998, 1999, 2000a). Furthermore the stronger the dependency, the worse the overall mood effects.

The nicotine abstinence syndrome is well documented, with cigarette smokers reporting a range of unpleasant moods when they have not smoked recently: heightened anger, stress, depression, irritability, restlessness and concentration difficulty (Hughes 1992; Hughes et al. 1990; Surgeon General 1990). These negative moods can develop within a comparatively brief period without nicotine, as any cigarette smoker who has to sit through a 'non-smoking' meeting can confirm. Significant increases in restlessness, irritability, poor concentration and reduced task performance can be demonstrated after one to two hours abstinence (Parrott et al. 1996, 2000). Withdrawal symptoms also become more severe under stressful than under relaxing conditions, so that the feelings of relief on nicotine reinstatement are correspondingly stronger (Parrott and Slater 2000). Smoking only generates mood changes in nicotine-deprived smokers, but these only represent the restoration of normal moods. When non-deprived smokers have a cigarette, their mood ratings remain unaltered (Parrott and Garnham 1998).

Regular smokers therefore experience fluctuating moods over the day. When smokers completed a brief mood self-rating for every cigarette over the day, normal moods were reported immediately after smoking, moods deteriorated in between cigarettes, and were normalized by the next cigarette (Parrott 1994). Adan and Sanchez-Turet (2000, p292) assessed moods at 14 time points over the day, and found that free-smoking smokers had more variable mood states than non-smoking controls, while their average moods were often worse: "Smokers have sub-optimal activation and mood states at certain times even under the influence of multiple doses of nicotine". Regular smokers thus suffer many periods of poor mood every day, with nicotine dependency comprising a direct cause of psychological distress (Parrott 1998, 1999, 2000a,b,c).

The degree of distress is also related to the heaviness of smoking. Around 15% of smokers use cigarettes intermittently, but these "chippers" report neither mood decrements when they abstain, nor mood gains when they smoke (Shiffman 1989). The absence of mood changes in "chippers" may help explain how they remain as occasional smokers (Parrott 1998). In contrast, heavy smokers generally report severe abstinence symptoms, and strong feelings of relief when they smoke, which is why they need to smoke so repetitively (Parrott 1998, 2000). This mood relief can be very reinforcing. Deprived smokers report immediate mood improvements on smoke inhalation (Warburton 1992), and similar gains in cognitive performance after just two puffs on the first cigarette of the day (Revell 1988). These positive psychobiological changes become conditioned with routine events such as meal/rest breaks, which is why smokers often see their cigarettes as everyday coping aids.

Nicotine dependency amongst disadvantaged smokers

Since nicotine dependency is the key to understanding cigarette smoking, strong abstinence symptoms can explain why smoking is so prevalent amongst the psychologically disadvantaged. The explanatory model proposed here is as follows. When any individual predisposed to poor moods takes up smoking, their negative feelings will become even stronger during nicotine abstinence. Thus in an individual prone to sadness and depression, depressive feelings will predominate during abstinence. Smoking will temporarily 'relieve' these aversive feelings, so that they readily become dependent upon nicotine for mood control. Yet the repeated experience of aversive moods in between cigarettes will paradoxically lead to increased depression. It should be emphasized that I am not aware of any study which has assessed mood state changes in novice/child smokers (i.e. the equivalent of Parrott (1994), with 10-14 year olds who are starting smoking; indeed any such study would raise serious ethical problems).

Patton et al. (1998) noted: "When you become a regular smoker, you quickly become dependent on nicotine, and nicotine withdrawal worsens the symptoms of depression". Kendler et al. (1993, p39) noted with adult smokers: "A progressive and substantial increase in risk for future episodes of major depression as a function of average daily cigarette consumption". Breslau and Johnson (2000, p1126) commented that: "The behavioural symptoms of nicotine dependence might drive the association with major depression". The strong abstinence symptoms of depressed smokers means that quitting will be very difficult, with a prolonged and severe abstinence syndrome (see earlier). Yet when depressed smokers attempt to quit, they benefit from both antidepressant medications and

nicotine replacement devices. Nicotine replacement ameliorates the abstinence symptoms, while antidepressant drugs such as bupropion alleviate the depressive feelings; hence the particular effectiveness of combination therapies for depressed smokers (Blondal, et al. 1999; Hurt et al. 1997; Kinnunen et al. 1996).

Nicotine dependency can also explain why emotionally labile or 'neurotic' individuals display an increased risk of smoking (Guildford 1966; Gilbert 1995; Parrott 1998). Individuals predisposed to emotional lability will develop strong feelings of restlessness and irritation during nicotine abstinence. Cigarettes reverse these stresses and strains, so that the neurotic individual readily becomes nicotine dependent, without realizing that their dependency is actually heightening their tension and anxiety problems (Parrott 1999, 2000c). Anxiolytic drugs such as buspirone can facilitate smoking cessation (West et al. 1991), probably by ameliorating the emotional lability and tension that characterizes the abstinence syndrome.

Nicotine dependency explains why so many psychobiological functions are impaired in cigarette smokers. For instance, smokers display significantly worse sleep than non-smokers (Wetter and Young 1994), but their sleep improves significantly six months after quitting (Wolter et al. 1996). Falling plasma nicotine levels over the night means that smokers suffer from increasing nicotine withdrawal, which probably disrupts sleep architecture. This also explains why the first cigarette of the day tends to be rated as the most 'satisfying' (Parrott 1998, 1999). Smokers also tend to suffer from low self-esteem, and guilt about their nicotine dependency. Self-efficacy is also impaired since when faced with problems, smokers often light up a cigarette to feel better, instead of directly tackling the problem; indeed this avoidance strategy is evident in schoolchildren who are smokers (Lloyd and Lucas 1997). There are therefore a wide range of inter-related factors, direct and indirect, cognitive and emotional, which explain why nicotine dependency heightens distress. These factors will often predominate amongst the disadvantaged.

Nicotine derived from cigarettes is not a medicine

Numerous claims have been made for the nicotine derived from cigarette smoke, that it can relieve stress, increase pleasure, aid thinking, foster creativity, relieve depression (Hughes 2000; Warburton 1992). But these apparently positive effects are all based upon acute-dose studies, where smokers feel and perform better when replete with nicotine, than when nicotine deprived (Gilbert 1995; Parrott 1998). Cross-sectional comparisons with non-smokers, and prospective studies of smokers over time, show

nicotine in a far more negative light. When Glass (1990) debated the possibility that nicotine/smoking might be being used as self-medication, he emphasized the absence of empirical evidence on this notion, and called for longitudinal studies. Many prospective studies have now been undertaken, but they have *all* failed to find any evidence of 'medicinal' gains. Instead they have found increased levels of stress and depression.

Another area where smoking/nicotine has been hypothesised to generate psychobiological gains is cortical arousal. Acute dose studies have reported that smokers display better alertness and cognitive functioning when replete with nicotine than when nicotine-deprived (Wesnes and Warburton 1983; Gilbert 1995; Parrott 1998; Revell 1988). But the brief periods of cognitive gain following smoke inhalation are counter-balanced by periods of cognitive loss during nicotine withdrawal, so that over the day the average cognitive ability levels of smokers and non-smokers are broadly similar (Parrott 1998). Self-medication has been debated as one possible reason for the high rates of smoking amongst adolescents with behavioural problems, and/or attention deficit disorder (Lambert and Hartsough 1998; Lynskey and Ferguson 1995). But again I am not aware of any prospective study showing that the uptake of smoking leads to behavioural benefits in problematic children/adolescents who take up smoking. It is most likely that their smoking will follow the pattern of dependency outlined earlier.

Cigarette-derived nicotine: a psychological damaging drug of addiction

Once the nicotine derived from cigarettes is conceptualised as a drug of dependency, its behavioural, cognitive and emotional effects become very straightforward to understand. The continual need to forestall or reverse abstinence symptoms explains why smokers follow such regular patterns of cigarette consumption over the day (Parrott 1994). Mood normalization also explains why the behaviour of unrestrained smokers is near-normal; in this respect nicotine is very different from other addictive drugs, such as opiates, amphetamine/cocaine and alcohol. The mood and cognitive effects of nicotine are also quite subtle, with only slight feelings of irritation during early abstinence so that its normative/restorative effects can be difficult to describe. Yet the 'relief' and 'contentment' after smoke inhalation accurately describe the reversal of incipient withdrawal symptoms while 'craving' describes the more urgent need to restore normality after longer periods without nicotine. This model also helps explain why acute nicotine boosts dopaminergic neural reward pathways, whereas chronic nicotine leads to quite different dopaminergic changes (Kirch 2000; Kirch et al. 1987). Thus smoke inhalation

in an abstinent smoker restores 'pleasure' to normal levels, but when a non-deprived smoker has another cigarette their self-rated pleasure remains unchanged/normal (Parrott and Garnham 1998). The disparate nature of the mood impairments during abstinence (irritability, anger, restlessness, poor concentration, sadness), and their reversal by smoke inhalation, helps explain why smoking has such a variety of seemingly contradictory effects. Nesbitt's Paradox is also readily explained. Smokers feel tired and stressed when their plasma nicotine falls, but smoking restores both functions in parallel; thus cortical arousal and emotional tension are normalized at the same time (Parrott 1998). It should be emphasized that the current article has only been concerned with the nicotine delivered from cigarettes. Tobacco smoke also contains many alkaloids and other ingredients which may also influence CNS activity (e.g. inhibition of MAO-B). Nicotine replacement devices are a proven aid for smoking cessation (Kinnunen et al. 1996), so that nicotine could be conceptualised as a 'medicine' for quitting smokers; however I am not aware of nicotine being licensed for any other disorders.

Rejection of the self-medication model for cigarette smoking has a number of practical implications. Smoking cessation packages should emphasize the psychological benefits of quitting. Many adult smokers mistakenly believe that they will become more anxious if they cannot smoke, and do not realize that they will become less stressed after quitting. Thus the promise of long-term mood gains could act as an incentive for those who have not yet decided to stop, while the likelihood of heightened stress and depression if they return to smoking may help prevent relapse. The chances of relapse are also highest in those situations where they have learned to associated smoke inhalation with mood relief (e.g. during rest breaks, following meals), so learning to weaken these associative links should be a key goal for any treatment package. One key area for future research is the initiation of dependence in young smokers, especially those from disadvantaged backgrounds. The main reasons for initial use are the desire to be accepted by their smoking peers, in order to be also seen as mature and socially attractive. But the initial period of occasional cigarette use is soon replaced by the early stages of nicotine dependency and regular patterns of smoking (McNeill 1991; Parrott 1998). Educational packages for schoolchildren should emphasize the adverse mood state consequences of using cigarettes. The restriction of access to tobacco products by children and adolescents is very important; if they can be prevented from experimenting with cigarettes before age 16, their chance of remaining non-smokers will be considerably enhanced. In overall conclusion, it is generally recognised that tobacco smoking is physically unhealthy. It needs to be far more

widely known that nicotine is also psychologically damaging.

References

- Adan A, Sanchez-Turet M (2000) Effects of smoking on diurnal variations of subjective activation and mood. *Hum Psychopharmacol* 15: 287-294.
- Anda RF, Croft JB, Felitti VJ, Nordenberg D, Giles WH, Williamson DF, Giovino GA (1999) Adverse childhood experiences and smoking during adolescence and adulthood. *JAMA* 282: 1652-1658.
- Blondal T, Gudmundsson LJ, Tomasson K, Jonsdottir D, Hilmarsdottir H, Kristjansson F, Nilsson F, Bjornsdottir US (1999) The effects of fluoxetine combined with nicotine inhalers in smoking cessation – a randomized trial. *Addiction* 94: 1007-1016.
- Breslau N, Johnson EO (2000) Predicting smoking cessation and major depression in nicotine-dependent smokers. *Am J Pub Health* 90: 1122-1127.
- Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P (1998) Major depression and stages of smoking: a longitudinal investigation. *Arch Gen Psychiatry* 55: 161-166.
- Carey MP, Kalra DL, Carey KB, Halperin S, Richards CS (1993) Stress and unaided smoking cessation: a prospective investigation. *J Consult Clin Psychol* 61: 831-838.
- Chassin L, Presson CC, Sherman SJ, Kim K (In Press) Long term psychological sequelae of smoking cessation and relapse. *Health Psychol*.
- Cohen S, Lichtenstein E (1990) Perceived stress, quitting smoking, and smoking relapse. *Health Psychol* 9: 466-478.
- Fant RV, Schuh KJ, Stizer ML (1995) Response to smoking as a function of prior smoking amounts. *Psychopharmacol* 119: 385-390.
- Gilbert DG (1995) Smoking: Individual Differences, Psychopathology, and Emotion. Taylor and Francis, London.
- Gilbert DG, McClernon FJ, Rabinovitch NE, Plath LC, Jensen RA, Meliska CJ (1998) Effects of smoking abstinence on mood and craving in men: influence of negative-affect-related personality traits, habitual nicotine intake and repeated measurements. *Personal & Individ Differences* 25: 399-423.
- Glass RM (1990) Blue mood, blackened lungs: depression and smoking. *JAMA* 264: 1583-1584.
- Glassman AH, Helzer JE, Covey LS, Cottler LB, Stetner F, Tipp JE, Johnson J (1990) Smoking, smoking cessation, and major depression. *JAMA* 264: 1546-1549.
- Goodman E, Capitman J (2000) Depressive symptoms and cigarette smoking among teens. *Pediatrics* 196: 748-755.
- Guildford JS (1966) Factors relating to successful abstinence from smoking. American Institute for Research, Pittsburgh, USA.
- Hall AM, Munoz RF, Reus VI, Sees KL (1993) Nicotine, negative affect, and depression. *J Consult & Clin Psychol* 61: 761-767.
- Hughes JR (1992) Tobacco withdrawal in self-quitters. *J Consult & Clin Psychol* 60: 689-697.
- Hughes JR (2000) Forward to: Nicotine in Psychiatry. Piasecki M, Newhouse PA (eds) American Psychiatric Press, Washington DC. pp xiii-xvii.
- Hughes JR, Higgins ST, Hatsukami D. (1990) Effects of abstinence from tobacco. In: Kowzowski LT (ed) *Recent Advances in Alcohol and Drug Problems*, Vol 10. Plenum, New York.

Hurt RD, Sachs DP, Glover ED (1997) A comparison of sustained release bupropion and placebo for smoking cessation. *New Eng J Med* 337: 1195-1202.

Ikard FF, Green DE, Horn D (1969) A scale to differentiate between types of smoking as related to the management of affect. *Internat J Addictions* 4: 649-659.

Johnson JG, Cohen P, Pine DS, Klein DF, Kasen S, Brook JS (2000) Association between cigarette smoking and anxiety disorders during adolescence and early childhood. *JAMA* 284: 2348-2351.

Kendler KS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC (1993) Smoking and major depression: a causal analysis. *Arch Gen Psychiatry* 50: 36-43.

Kinnunen T, Doherty K, Miletello FS, Garvey AJ (1996) Depression and smoking cessation: effects of nicotine replacement. *J Consult & Clin Psychol* 64: 791-798.

Kirch DG (2000) Nicotine and major mental disorders. In: *Nicotine in Psychiatry*. Piasecki M, Newhouse PA (eds) American Psychiatric Press, Washington DC, pp 111-130.

Kirch DG, Gerhardt DA, Shelton RC (1987) Effect of chronic nicotine administration on monoamine and monoamine metabolite concentration in the rat brain. *Clin Neuropharmacol* 10: 376-383.

Lambert NM, Hartsough CS (1998) Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. *J Learn Disabil* 31: 533-544.

Lloyd B, Lucas K (1997) *Smoking in Adolescence: Images and Identities*. Routledge, London.

Lynsky MT, Ferguson DH (1995) Childhood conduct problems, attention deficit behaviors, and adolescent alcohol, tobacco, and illicit drug use. *J Abnorm Child Psychol* 23: 281-302.

McGee R, Williams S, Poulton R, Moffitt T (2000) A longitudinal study of cannabis use and mental health from adolescence to early adulthood. *Addiction* 95: 491-504.

McNeill AD (1991) The development of dependence on smoking in children. *British Journal of Addiction*. 86: 589-592.

Mitic WR, McGuire DP, Neumann B (1985) Perceived stress and adolescents' cigarette use. *Psychol Reports* 57: 1043-1048.

Parrott AC (1994) Individual differences in stress and arousal during cigarette smoking. *Psychopharmacol* 115: 389-396.

Parrott AC (1995) Smoking cessation leads to reduced stress, but why? *Internat J Addictions* 30: 1509-1516.

Parrott AC (1998) Nesbitt's Paradox resolved? Stress and arousal modulation during cigarette smoking. *Addiction* 93: 27-39.

Parrott AC (1999) Does cigarette smoking cause stress? *Amer Psychol* 54: 817-820.

Parrott AC (2000a) Nicotine/cigarette dependency: a cause of depression? *Int J Neuropsychopharmacol* 3: s324.

Parrott AC (2000b) Smoking and adverse childhood experiences: a reply to Anda. *JAMA* 283: 1959.

Parrott AC (2000c) Cigarette smoking does cause stress. *Amer Psychol* 55: 1159-1160.

Parrott AC, Garnham NJ (1998) Comparative mood states and cognitive skills of cigarette smokers, deprived smokers, and non-smokers. *Hum Psychopharmacol* 13: 367-376.

Parrott AC, Slater M (2000) Cigarette abstinence symptoms under stressful and relaxing conditions. *Psychobiol News* 34: 13.

Parrott AC, Garnham NJ, Wesnes K, Pincock C (1996) Cigarette smoking and abstinence: comparative effects upon cognitive task performance and mood state over 24 hours. *Hum Psychopharmacol* 11: 391-400.

Parrott AC, Thurkle J, Ward M (2000) Nicotine abstinence in regular smokers: mood and cognitive performance deficits after just one hour. *J Psychopharmacol* 14: a12.

Patton GC, Carlin JB, Coffey C, Wolfe R, Hibbert M, Bowes G (1998) Depression, anxiety, and smoking initiation: a prospective study over 3 years. *Amer J Public Health* 88: 1518-1522.

Perkins KA (1999) Baseline-dependency of nicotine effects: a review. *Behav Pharmacol* 10: 597-615.

Piasecki M, Newhouse PA (2000) *Nicotine in Psychiatry*. American Psychiatric Press, Washington DC.

Revell AD (1988) Smoking and performance: a puff-by-puff analysis. *Psychopharmacol* 96: 563-565.

Russell MAH, Peto J, Pavel VA (1974) The classification of smoking by a factorial structure of motives. *J Royal Stat Soc* 137: 313-346.

Schiffman S (1989) Tobacco chippers: individual differences in tobacco dependence. *Psychopharmacol* 97: 539-547.

Surgeon General (1988) *Nicotine Addiction*. US Government Printing Office, Washington DC.

Surgeon General (1990) *The Health Benefits Smoking Cessation*. US Government Printing Office, Washington DC.

Warburton, DM (1992) Smoking within reason. *J Smoking-related Disord* 3: 55-59.

Wesnes K, Warburton DM (1983) Smoking, nicotine, and human performance. *Pharmacol & Therapeutics* 21: 189-208.

West R, Hajek P (1997) What happens to anxiety levels on giving up smoking? *Amer J Psychiatry* 154: 1589-1592.

West R, Hajek P, McNeill A (1991) Effects of buspirone on cigarette withdrawal symptoms and short-term abstinence rates in a smokers clinic. *Psychopharmacol* 104: 91-96.

Wetter DW, Young TB (1994) The relation between cigarette smoking and sleep disturbance. *Preventative Med* 23: 328-334.

Wills TA (1986) Stress and coping in early adolescence: relationships to smoking and alcohol use in urban school samples. *Health Psychol* 5: 503-529.

Wolter T, Hauri PJ, Schroeder DR (1996) Effects of 24-hour nicotine replacement on sleep and daytime activity during smoking cessation. *Preventative Med* 25: 601-610.

Wu LT, Anthony JC (1999) Tobacco smoking and depressed mood in late childhood and early adolescence. *Amer J Public Health* 89: 1837-1840.

Substance P and Substance P Receptor Antagonists in the Pathogenesis and Treatment of Affective Disorders

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Summary

Substance P (SP) is a neuropeptide which is widely distributed in the periphery and the central nervous system (CNS), where it is co-localised with other neurotransmitters such as serotonin or dopamine and where it acts as a neuromodulator. SP has been proposed to play a role in the aetiopathology of asthma, inflammatory bowel disease, emesis, psoriasis, as well as neuropsychiatric disorders including pain syndromes (e.g. migraine and fibromyalgia) and affective disorders, anxiety disorders, schizophrenia and Alzheimer's disease. This review focuses on the role of SP in the pathogenesis of affective disorders. It summarises the current knowledge on measurements of SP in the CSF and serum in patients with depressive disorders or fibromyalgia, effects of SP-application in humans, SP-receptor expression in postmortem brains and the modulation of SP levels in the course of antidepressant treatment. It also discusses the promise of substance P-receptor antagonists (SPA) for the treatment of affective disorders and their proposed mechanism of action. In summary, much more research is needed to elucidate the role of SP in the pathogenesis of depression. SPA are promising as future drugs for the treatment of affective disorders, but current clinical trials have yet to be completed to draw a firm conclusion.

Key words: substance P, neurokinin1-receptor, affective disorders, depression, review.

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Introduction

The undecapeptide Substance P (SP) belongs to the group of neurokinin (tachykinin) peptides. This group of peptides, which are defined by the common C-terminal amino acid sequence Phe-X-Gly-Leu-Met-NH₂, also includes neurokinin-A (NKA) and neurokinin-B (NKB) among several other neuropeptides (Table 1). SP can be synthesized from three alternatively spliced forms of the preprotachykinin-A (PPT-A) gene (Krause et al. 1987), with the β- and γ- splice variants also containing the coding sequence for NKA. SP exerts its effects by binding to the neurokinin (NK)-receptors: SP preferentially binds to the NK-1-receptor (SP-receptor) and with lower affinity to the NK-2- and NK-3-receptors, which preferentially bind NKA and NKB, respectively (Otsuka and Yoshioka 1993). The SP-receptor is a G-protein-coupled receptor, which upon binding of SP activates several second messenger systems, protein kinases and transcription factors including calcium, inositol triphosphate, p42/44 and p38 stress-regulated kinases, protein kinase C and the transcription factor nuclear factor kappa B (Otsuka and Yoshioka 1993; Lieb et al. 1997, 1998; Fiebich et al. 2000). After release from nerve terminals, SP is rapidly degraded by several proteases including neutral endopeptidase 24.11, metalloendopeptidase, dipeptidyl-peptidase IV and angiotensin-converting enzyme (ACE).

Table 1

Amino acid sequence of SP, NKA and NKB

Neurokinin	Sequence
Substance P	Arg-Pro-Ly-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH ₂
Neurokinin A	His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH ₂
Neurokinin B	Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH ₂

SP is the most abundant neurokinin and is involved in the regulation of many physiological processes, e.g. in the gut, the bronchial and the vascular system (Quartara and Maggi 1998). In the CNS, SP-containing neurons are distributed in distinct neuronal networks. They are found for example in the midbrain and basal ganglia, the hypothalamus, the limbic system including the hippocampus and amygdala and the spinal cord (Pioro et al. 1990). SP is co-localised with other neurotransmitters and has neuromodulatory effects. Examples are co-localisations with

serotonin in the ncl. raphe, with dopamine in the midbrain and striatum, with GABA and acetylcholine in the cortex and with corticotropin releasing hormone (CRH) in the hypothalamus (Otsuka and Yoshioka 1993; Sergeyev et al. 1999). Examples for direct neuromodulatory effects of SP are the regulation of acetylcholine release in the human cortex (Feuerstein and Seeger 1997) and the modulation of noradrenergic neurotransmission in the locus coeruleus (Hahn and Bannon 1999).

Because of its wide distribution, its neuromodulatory effects and its involvement in neurogenic inflammation (Lieb et al. 1996, 1997; Richardson and Vasko 2002), SP has been proposed to be involved in the aetiopathology of different pathophysiological conditions. Examples are asthma, inflammatory bowel disease, emesis and psoriasis. Moreover, SP has been suggested to be important in the aetiopathology of psychiatric disorders including pain syndromes (e.g. migraine and fibromyalgia), neurodegenerative disorders (Barker 1991), affective disorders, anxiety disorders including social phobia, and schizophrenia (Quartara and Maggi 1998; Rupniak and Kramer 1999; Stout et al. 2001; Lieb et al. 2002b,c; Rupniak 2002a,b).

This review focuses on the role of SP in the pathogenesis of affective disorders. It summarises the current knowledge on measurements of SP in the cerebrospinal fluid (CSF) and serum of patients with depressive disorders or fibromyalgia, effects of SP-application in humans, SP-receptor expression in *post mortem* brains and the modulation of SP levels in the course of antidepressant treatment. The review also discusses the promise of substance P-receptor antagonists (SPA) for the treatment of affective disorders and their proposed mechanism of action.

The role of SP in the pathology of affective disorders – what is the evidence from human studies?

The following approaches have been used to study the role of SP in the aetiopathology of affective disorders: The measurement of SP levels in the CSF and serum of affected patients, the investigation of the effects of SP-application in healthy subjects, the investigation of the effects of a polymorphism in the SP-degrading enzyme ACE, as well as the determination of SP-receptors in *post mortem* brains of depressed patients.

• SP in the CSF of depressed patients

Rimon et al. measured SP in the CSF of 12 depressed and 12 schizophrenic patients as well as 15 controls (Rimon et al. 1984). They found significantly increased concentrations of SP in the depressed patients compared to the schizophrenic patients and the controls. Furthermore, they found the SP(1-7)-fragment in the CSF of

depressed patients, which they interpreted to be of possible pathogenic relevance. Another study by Berrettini et al., however, could not confirm these findings. They measured SP levels in the CSF of 19 inpatients (3 acutely and unmedicated manic, 12 depressed and 4 euthymic patients) and 29 outpatients (15 unmedicated bipolar patients and 24 lithium-treated bipolar patients) and found them no different to levels in normal controls (Berrettini et al. 1985).

These divergent results have been attributed to methodological differences. Toresson et al. (1988) even questioned whether SP can be reliably measured in CSF. They reported that "undeca-SP" is not present in measurable concentrations in the CSF (less than 0.1 pmol/l), but that instead an N-terminally elongated form of SP can be measured by a combined HPLC and RIA method. In an open study of nine unmedicated depressed inpatients, Martensson et al. (1989) showed that the mean level of N-terminally extended SP in the CSF was unaffected by 6-week fluoxetine treatment, but that pre-treatment levels correlated significantly with the pre-treatment level of the norepinephrine metabolite 4-hydroxy-3-methoxyphenyl glycol (HMPG). They concluded that an influence on the noradrenergic system, directly or indirectly, may perhaps be a prerequisite for an antidepressant effect (Martensson et al. 1989).

Elevated levels of CSF SP have been demonstrated in the fibromyalgia syndrome (FMS), a chronic pain syndrome whose pathophysiological mechanisms are often related to depression (Ackenheil 1998). As shown in five independent reports, patients with FMS exhibit significantly elevated levels of CSF SP, with two to three fold higher values among the patients than the controls (e.g. Vaeroy et al. 1988; Russell et al. 1994; reviewed in Russell 2002). Further investigations showed that the elevated CSF SP levels in people with FMS are quite stable, and that they might be integrally related to changes in the severity of the symptomatic pain (for review see Russell 2002).

• Serum levels of SP in response to stress and in depressed patients

Serum levels of SP have been determined in response to acute and chronic stress situations. In a first study, serum levels of SP were measured in 47 inexperienced tandem-parachutists 2 hours before, immediately after and 1 hour after a parachute jump. Although SP serum concentrations were unaffected by the jump stress, subjects with high anxiety displayed higher plasma SP levels at all three time points as compared to "low anxiety jumpers" (Schedlowski et al. 1995). In another study, SP levels were measured in 22 civilians during and after a war attack with Scud missiles and were found to be elevated (Weiss et al. 1996).

In a study with 23 patients suffering from major depression, Bondy and colleagues measured serum SP levels before and after two and four weeks of antidepressant therapy (Bondy et al. In Press). They found that the mean baseline SP serum concentrations were significantly higher in depressed patients as compared to 33 controls. In both patients and controls, SP remained relatively constant over a period of four weeks. At least to our knowledge, there are no other published reports on SP serum levels in patients with affective or other neuropsychiatric disorders.

• Intravenous application of SP

Intravenously given SP has been shown to stimulate secretion of adrenocorticotrophic hormone (ACTH) and cortisol in healthy male subjects (Coiro et al. 1992). We investigated the effects of SP on sleep, nocturnal hormone secretion and mood in a double-blind placebo-controlled study in 12 healthy male subjects (Lieb et al. 2002a). Infusion of SP in four blocks of 20 minutes between 10 p.m. and 1 a.m. led to a significant worsening of the mood of the subjects as compared to placebo directly after the infusion and in the following morning. With respect to sleep parameters, SP infusion caused an increase of REM latency and time awake during the SP-infusion intervals, and caused increased stage 1 sleep in the first part of the night. In addition, cortisol and TSH secretion was increased. Although it has been controversially discussed whether SP is able to penetrate the blood brain barrier (Ermisch et al. 1985; Freed et al. 2002), we interpreted these data as evidence for a central arousing effect of SP and as support for the idea that SP might be a possible depressogenic substance. However, further data have to substantiate these findings, and mood changes have to be demonstrated in patients with affective disorders.

• Effect of the ACE polymorphism

Arinami and colleagues investigated whether a polymorphism in the gene coding for the angiotensin converting enzyme (ACE), which may break down SP, is associated with affective disorders in humans (Arinami et al. 1996). The authors found that the D/D genotype of the ACE-gene, which may cause higher SP concentrations in the brain, is more frequently found in depressed Japanese patients as compared to controls. However, this was not replicated by subsequent studies (e.g. Pauls et al. 2000; Baghai et al. 2001; Hong et al. 2002). Baghai and colleagues, however, found that the D-allele of the ACE-gene might positively influence therapeutic outcome: after four weeks of treatment, Caucasian D-allele carriers showed lower HAM-D17 scores, more remissions and a significantly shorter duration of hospitalisation than I/I-genotypes (Baghai et al. 2001). Hong et al. (2002), though, were unable to replicate Baghai's finding in their study with moderately depressed

Chinese patients: they could not show any significant difference in clinical manifestations or antidepressant response comparing the three ACE genotypes, D/D, I/D and I/I.

• NK-1-receptors in post mortem brain

Burnet and Harrison (2000) determined the density of NK-1-receptors in the anterior cingulate cortex in *post mortem* brains of patients with unipolar depression, bipolar disorder, schizophrenia and controls. Although they did not find differences in the total density of receptors between the four groups, they observed a relatively increased density of NK-1-receptors in deep laminae in unipolar depressed patients. In a second study, Stockmeier and colleagues measured NK-1-receptor binding in the rostral orbitofrontal cortex (Brodmann's area 47) in *post mortem* brains of 12 patients with major depressive disorder and 11 normal subjects without psychiatric disorders (Stockmeier et al. 2002). In contrast to the above study, they found decreased binding of [¹²⁵I]BH-substance P to NK-1-receptors across all cortical layers reflecting a decreased density of NK-1-receptors in depressed patients. Differences between the study by Burnet and Harrison (2000) and the study by Stockmeier et al. (2002) may be due to methodological differences, the different brain areas investigated, the possible influences by medication status and agonal state as well as post mortem delay.

Are substance P receptor antagonists (SPA) effective antidepressants?

Because of the well characterised role of SP in nociceptive signal transmission (for review see Quartara and Maggi 1998 and Snijdelaar et al. 2000), SP-receptor antagonists (SPA) have first been evaluated in the treatment of pain. However, SPA such as CP99994, CP122721, MK-869, LY303870, RPRP100893, L758298 or GR205171 showed no or only little effect in the treatment of pain including dental pain, migraine, rheumatoid arthritis or post-herpetic neuralgia (Rupniak and Kramer 1999; Hill 2000; Rupniak and Hill 2000). Similarly, a double-blind, placebo-controlled, randomised, 8-week crossover study conducted in 1994 by Littman and colleagues in 30 FMS patients with 50 mg bid of the SPA CJ-11974 showed no effects on pain ratings, anxiety or depression (Littman et al. 1999). The only significant effect was an improvement of dysesthesia in the hands and feet of FMS patients.

Based on the co-localisation of SP and dopamine in the nigrostriatal system and the modulatory effects of SP on dopaminergic neurotransmission, it has been speculated that SPA might be effective in the treatment of schizophrenia. However, a recent exploratory, 4-week placebo- and haloperidol-controlled trial with 400 mg of the SPA MK-869 did not show antipsychotic

activity in patients with schizophrenia (Kramer et al., unpublished data).

To date, SPA are developed as antidepressants, and the current state of the art is discussed in the following section. An additional field of development is the treatment of chemotherapy-induced emesis with MK-869 from Merck (Rupniak and Kramer 1999; Navari et al. 1999; van Belle et al. 2002).

The rationale for conducting a clinical depression trial with an SPA had its origins in neuroanatomical studies showing that NK-1 receptors are located in areas involved in emotional processes (e.g. amygdala, hippocampus and hypothalamus), in the observation that SP injection in these areas produces a range of fear-related behaviours and that SP content in these areas changes in response to stress, and in preclinical findings showing that SPA attenuate stress-induced neurochemical, cardiovascular and behavioural defence responses (reviewed in Rupniak 2002b).

The first study that showed antidepressant effects of a SPA was the study performed by Kramer et al. (1998). These authors found that the SPA MK-869 showed as good clinical efficacy in the treatment of depression and anxiety as paroxetine, a selective serotonin reuptake inhibitor (for structure of MK-869 see Figure 1). The authors tested MK-869 in a randomised, double-blind and placebo-controlled multicentre study with 213 depressed out-patients. The patients were randomly assigned to daily treatment with 300 mg MK-869, 20 mg paroxetine or placebo. They were treated for six weeks, primary outcome measures were the Hamilton Depression Scale (HADS) and the Hamilton Anxiety Scale as well as the CGI-S. MK-869 and paroxetine were more effective than placebo: 54% of the patients treated with MK-869 as compared to 28% treated with placebo responded to the treatment and 43% of the patients treated with MK-869 in comparison to 17% with placebo had a complete remission of depression (HADS < 10). MK-869 was very well tolerated: Side effects did not occur

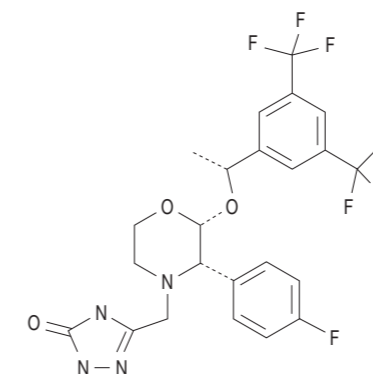


Figure 1
Structure of the SPA MK-869

more often than with placebo treatment. This was also the case for sexual dysfunction which in contrast occurred in 26% of the patients treated with paroxetine. Treatment with MK-869 was not more often stopped than with placebo.

The same authors also conducted a follow-up dose-finding study with more than 800 depressed patients. In this study, MK-869 as well as the reference antidepressant fluoxetine were not superior to placebo treatment (discussed in Enserink 1999). However, Rupniak and Kramer commented on this unpublished study that *post hoc* analyses had shown antidepressant efficacy of MK-869 in the subset of severely depressed patients (HADS > 25) (Rupniak and Kramer 1999). Merck conducted another randomised, double-blind and placebo-controlled study to investigate the efficacy of a new SPA, L-759274, at a dosage of 40 mg in 117 severely depressed patients (mean HADS = 28). As in the MK-869 study of 1998, SPA treatment was significantly superior to placebo treatment (Kramer et al. Submitted, presented at the American College of Neuropsychopharmacology meeting in December 2001). To sum up, in two high-quality (since randomised, double-blind and placebo-controlled) studies, an antidepressant efficacy of a SPA could be demonstrated. Further clinical studies are currently in progress.

Possible mechanisms of action of SPA

Several preclinical approaches have been followed to investigate possible mechanisms of action of SPA:

- Comparison of the efficacy of SPA with established antidepressants in animal models of affective disorders
- Comparison of the consequences of a genetic deletion of the NK-1 receptor ("NK-1 receptor-knockout mice") with established antidepressants in animal models of affective disorders
- Investigation of the impact of SPA or of NK-1 receptor deletion on the serotonergic and noradrenergic system.

Despite the well-known disadvantages of animal models in general, the first and second approach showed that the pharmacological blockade as well as the genetic deletion of the NK-1 receptor led to a behavioural profile which resembles that seen with established antidepressants such as the selective serotonin reuptake inhibitors (SSRI): examples are the inhibition of aggression and neonatal vocalization by maternal separation and the increase in the duration of struggle in the forced swim test in SPA-treated animals and NK-1 receptor knockout mice (de Felipe et al. 1998; Rupniak et al. 2000, 2001; Santarelli et al. 2001). In preclinical assays that require repeated administration of antidepressant drugs (which may probably be more clinically relevant), an antidepressant-like activity of SPA in rat assays of learned helplessness (McElroy et al. 1999) and

chronic mild stress (Papp et al. 2000) was shown. However, considering the high species variation in NK-1 receptor pharmacology it is currently not clear whether these effects are really the consequence of selective NK-1 receptor blockade or rather of an unselective blockade of ion channels (Rupniak 2002a).

In several recent studies, the effects of SPA or genetic deletion of the NK-1 receptor on the serotonergic and noradrenergic system have been investigated in order to clarify whether antidepressant effects might be due to influences on one or both of these neurotransmitters systems. The rationale for these investigations is the fact that approximately 50% of dorsal raphe serotonergic neurons coexpress SP (Sergeyev et al. 1999) and that noradrenergic neurons originating in the locus coeruleus are innervated by SP-containing neurons and express NK-1 receptors on their cell bodies (Hahn and Bannon 1999). As summarized in Rupniak (2002b), SPA have no relevant affinity to monoamine oxidase A and B, norepinephrine and serotonin reuptake sites or monoamine receptors, and do not cause downregulation of adrenergic beta-receptors (Kramer et al. 1998). Table 2 shows a summary of the effects of chronic pharmacological blockade or genetic deletion of NK-1 receptors on serotonergic neuronal function. SPA as well as genetic deletion influence serotonergic neuronal function, but in a manner that is distinct from that seen with SSRI: SPA and genetic deletion do not increase serotonin efflux in brain regions innervated by serotonergic neurons (Kramer et al. 1998; Millan et al. 2001). Another difference is that SPA and genetic deletion cause a marked increase in the firing rate of dorsal raphe neurons (Santarelli et al. 2001; Conley et al. 2002). Additionally, a desensitisation of the 5-HT_{1A} autoreceptor (that is also seen after chronic treatment with SSRI), could be observed in NK-1 knockout mice (Santarelli et al. 2001; Froger et al. 2001), although it was not seen after chronic SPA application (Conley et al. 2002).

Table 2

Comparison of the effects of chronic pharmacological blockade or genetic deletion of NK1 receptors with SSRI on serotonergic neuronal function (modified according to Rupniak 2002a)

Parameter	SSRI	NK1R-/- mouse	SPA
Serotonin efflux	increase	not changed	not changed
5-HT _{1A} autoreceptor	desensitized	desensitized	not changed
Neuronal firing rate	not changed	increase	increase

In contrast to their lack of effect on serotonin efflux, other studies showed that SPA increase norepinephrine efflux in the hippocampus and frontal cortex (Millan et al. 2001) and alter the firing rate of locus coeruleus neurons

(Millan et al. 2001; Maubach et al. 2002). Modulation of the noradrenergic system may therefore also be relevant for the antidepressant effects of SPA.

Very recent studies, however, indicate that SPA may exert their antidepressant effects not only via modulation of monoamine systems. Possible other mechanisms of action are an increase of hippocampal neurogenesis (van der Haart et al. 2002) or a modulation of the HPA axis (Lieb et al. 2002a; Rupniak 2002a). Further studies are needed to confirm these findings.

SP and its receptor and treatment with antidepressants

• Preclinical studies

In preclinical research, there have been efforts to explain the mood stabilizing properties of antidepressants and lithium salts by modulation of SP- or NKA-neurotransmission. Studies in rats have shown that chronic application of tricyclic antidepressants over 40 days causes a downregulation of SP in the limbic system (Shirayama et al. 1996). Since three other studies did not show a modulation of SP content after application of drugs for 14 days, it might be speculated that long-term treatment is necessary to induce adaptive changes (reviewed in Stout et al. 2001). Subchronic lithium treatment, in contrast, was found to increase preprotachykinin mRNA expression as well as SP- and NKA-like immunoreactivity in the striatum and frontal cortex of rats (Hong et al. 1983; Sivam et al. 1989; Mathe et al. 1990, 2001). In a recently published study, the effect of 6-week application of lithium in Flinders Sensitive Line (FSL) rats, an animal model of depression, was compared to control rats (Husum et al. 2001). SP- and NKA-like immunoreactivity was markedly decreased in the striatum and increased in frontal cortex in the FSL-rats, and this effect was abolished by lithium treatment.

We have recently observed that the antidepressant St. John's wort causes a significant and dose-dependent inhibition of cytokine gene expression induced by SP (Fiebich et al. 2001). In a further study (Lieb et al. In Press), we observed that valproic acid (VPA), a mood stabiliser successfully being used for the treatment of bipolar affective disorders (Grunze et al. 1999), downregulated SP-induced expression of the cytokine interleukin 6 (IL-6), which has been shown to be increased during the acute depressed state (e.g. Frommberger et al. 1997). This inhibitory effect of VPA was due to an inhibition of protein kinase C (PKC) which has been proposed to be a key element in mediating antimanic effects of mood stabilizers (Manji and Lenox 1999). Furthermore, VPA caused a downregulation of the expression of the NK-1-receptor. These results of an inhibition of SP-induced effects by VPA are in line with results

obtained in healthy young men where VPA blocked SP-induced ACTH-synthesis (Coiro et al. 1992). In conclusion, preclinical data suggest that downregulation of SP synthesis or the inhibition of SP-induced gene expression might at least in part contribute to the clinical effectiveness of antidepressant drugs or mood stabilising agents. However, study results are in part conflicting and much more research is needed.

• Clinical studies

Bondy and colleagues measured SP serum levels in depressed patients during a 4-week antidepressant drug trial (Bondy et al. In Press). Although they did not observe a change in SP serum levels during therapy in the total patient group, they found that 37% of them showed a decrease in SP levels during therapy which was positively correlated to drug response. The authors speculated that these patients who showed a decrease of SP in relation to a good drug response might be a subgroup of patients in which SP plays a key role in the pathogenesis of their disorder and who might possibly be suitable candidates for the treatment with SPA.

The findings by Bondy and colleagues are in line with a recent study performed by our group (Lieb et al. Submitted b). We determined SP serum levels before and during a 9-week drug trial with paroxetine in combination with lamotrigine or placebo in 40 patients with a major depressive episode. In the total group of patients, the mean SP levels did not change during the 9-week trial. However, therapy-responders and non-responders significantly differed in SP serum levels: responders started with higher SP levels which decreased during drug therapy, whereas non-responders had lower SP levels which increased at the beginning of drug therapy. We speculated that SP serum levels might be a possible predictor of antidepressant response, and that eventually the non-responders with increasing SP levels might benefit from the additional application of a SPA.

Conclusions

There are now several reports from preclinical and clinical research which investigated a potential role of SP in affective disorders. However, study results are still insufficient and in part conflicting. Therefore, much more research is needed to establish a clear argument for a role of SP in the pathogenesis of affective disorders. SPA are promising as future drugs for the treatment of affective disorders, as it was demonstrated in two randomised, double-blind and placebo-controlled studies that SPA are superior to placebo in treating depression. Very recent research showed that SPA may act by modulating the serotonergic and noradrenergic system in a way which is different to that seen by classical antidepressant drugs. However, current clinical

trials have yet to be completed to make a firm conclusion regarding the potential of SPA as antidepressant drugs.

References

- Ackenheil M (1998) Genetics and pathophysiology of affective disorders: relationship to fibromyalgia. *Z Rheumatol* 57 (Suppl 2): 5-7.
- Arinami T, Li L, Mitsushio H, Itokawa M, Hamaguchi H, Toru M (1996) An insertion/deletion polymorphism in the angiotensin converting enzyme gene is associated with both brain substance P contents and affective disorders. *Biol Psychiatry* 40: 1122-1127.
- Baghai TC, Schule C, Zwanzger P, Minov C, Schwarz MJ, de Jonge S, Rupprecht R, Bondy B (2001) Possible influence of the insertion/deletion polymorphism in the angiotensin I-converting enzyme gene on therapeutic outcome in affective disorders. *Mol Psychiatry* 6: 258-259.
- Barker R (1991) Substance P and neurodegenerative disorders. A speculative review. *Neuropeptides* 20: 73-78.
- Berrettini WH, Rubinow DR, Nurnberger JI, Simmons-Alling S, Post RM, Gershon ES (1985) CSF substance P immunoreactivity in affective disorders. *Biol Psychiatry* 20: 965-970.
- Bondy B, Baghai TC, Minov C, Schule C, Schwarz MJ, Zwanzger P, Rupprecht R, Möller HJ (In Press) Substance P serum levels are increased in major depression: preliminary results. *Biol Psychiatry*.
- Burnet PW, Harrison PJ (2000) Substance P (NK1) receptors in the cingulate cortex in unipolar and bipolar mood disorder and schizophrenia. *Biol Psychiatry* 47: 80-83.
- Coiro V, Capretti L, Volpi R, Davoli C, Marcato A, Cavazzini U, Caffarri G, Rossi G, Chiodera P (1992) Stimulation of ACTH/cortisol by intravenously infused substance P in normal men: inhibition by sodium valproate. *Neuroendocrinology* 56: 459-463.
- Conley RK, Cumberbatch MJ, Mason GS, Williamson DJ, Harrison T, Locker K, Swain C, Maubach K, O'Donnell R, Rigby M, Hewson L, Smith D, Rupniak NM (2002) Substance P (neurokinin 1) receptor antagonists enhance dorsal raphe neuronal activity. *J Neurosci* 22: 7730-7736.
- De Felipe C, Herrero JF, O'Brien JA, Palmer JA, Doyle CA, Smith AJH, Laird JMA, Belmonte C, Cervero F, Hunt SP (1998) Altered nociception, analgesia and aggression in mice lacking the receptor for substance P. *Nature* 392: 394-397.
- Enserink M (1999) Can the placebo be the cure? *Science* 284: 238-240.
- Ermisch A, Ruhle HJ, Landgraf R, Hess J (1985) Blood-brain barrier and peptides. *J Cereb Blood Flow Metab* 5: 350-357.
- Feuerstein TJ, Seeger W (1997) Modulation of acetylcholine release in human cortical slices: possible implications for Alzheimer's disease. *Pharmacol Ther* 74: 333-347.
- Fiebich BL, Schleicher S, Butcher RD, Craig A, Lieb K (2000) The neuropeptide substance P activates p38 mitogen-activated protein kinase resulting in IL-6 expression independently from NF-kappaB. *J Immunol* 165: 5606-5611.
- Fiebich BL, Höllig A, Lieb K (2001) Inhibition of Substance P-induced cytokine synthesis by St. John's wort extracts. *Pharmacopsychiatry* 34 (Suppl 1): S26-S28.
- Freed AL, Audus KL, Lunte SM (2002) Investigation of substance P transport across the blood-brain barrier. *Peptides* 23: 157-165.
- Froger N, Gardier AM, Moratalla R, Alberti I, Lena I, Boni C, De Felipe C, Rupniak NM, Hunt SP, Jacquot C, Hamon M, Lanfumey L (2001) 5-hydroxytryptamine (5-HT)_{1A} autoreceptor adaptive

changes in substance P (neurokinin 1) receptor knock-out mice mimic antidepressant-induced desensitization. *J Neurosci* 21: 8188-8197.

Frommberger UH, Bauer J, Haselbauer P, Fraulin A, Riemann D, Berger M (1997) Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. *Eur Arch Psychiatry Clin Neurosci* 247: 228-233.

Grunze H, Erfurth A, Amann B, Giupponi G, Kammerer C, Walden J (1999) Intravenous valproate loading in acutely manic and depressed bipolar I patients. *J Clin Psychopharmacol* 19: 303-309.

Hahn MK, Bannon MJ (1999) Stress-induced C-fos expression in the rat locus coeruleus is dependent on neurokinin 1 receptor activation. *Neuroscience* 94: 1183-1188.

Hart van der MGC, Czeh B, Biurrun de G, Michaelis T, Watanabe T, Natt O, Frahm J, Fuchs E (2002) Substance P receptor antagonist and clomipramine prevent stress-induced alterations in cerebral metabolites, cytochrome in the dentate gyrus and hippocampal volume. *Molecular Psychiatry* 7: 933-941.

Hill R (2000) NK1 (substance P) receptor antagonists – why are they not analgesic in humans? *Trends Pharmacol Sci* 21: 244-246.

Hong JS, Tilson HA, Yoshikawa K (1983) Effects of lithium and haloperidol administration on the rat brain levels of substance P. *J Pharmacol Exp Ther* 224: 590-593.

Hong CJ, Wang YC, Tsai SJ (2002) Association study of angiotensin I-converting enzyme polymorphism and symptomatology and antidepressant response in major depressive disorders. *J Neural Transm* 109: 1209-1214.

Husum H, Vasquez PA, Mathe AA (2001) Changed concentrations of tachykinins and neuropeptide Y in brain of a rat model of depression. Lithium treatment normalizes tachykinins. *Neuropsychopharmacology* 24: 183-191.

Kramer MS, Cutler N, Feighner J, Shrivastava R, Carman J, Sramek JJ, Reines SA, Liu G, Snavely D, Wyatt-Knowles E, Hale JJ, Mills SG, MacCoss M, Swain CJ, Harrison T, Hill RG, Hefti F, Scolnick EM, Cascieri MA, Chicchi GG, Sadowski S, Williams AR, Hewson L, Smith D, Carlson EJ, Hargreaves RJ, Rupniak NMJ (1998) Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science* 281: 1640-1645.

Kramer MS, Winokur A, Kelsey J, Preskorn SH, Rothschild A, Snavely D, Ghosh K, Ball WA, Reines S, SPA Depression Study Group. (Submitted) Demonstration of the efficacy and safety of a second novel substance P (NK1) receptor antagonist (SPA) in major depression.

Krause JE, Chirgwin JM, Carter MS, Xu ZS, Hershey AD (1987) Three rat preprotachykinin mRNAs encode the neuropeptides substance P and neurokinin A. *Proc Natl Acad Sci USA* 84: 881-885.

Lieb K, Fiebich BL, Busse-Grawitz M, Hull M, Berger M, Bauer J (1996) Effects of substance P and selected other neuropeptides on the synthesis of interleukin-1 beta and interleukin-6 in human monocytes: a re-examination. *J Neuroimmunol* 67: 77-81.

Lieb K, Fiebich BL, Berger M, Bauer J, Schulze-Osthoff K (1997) The neuropeptide substance P activates transcription factor NF-kappaB and kappaB-dependent gene expression in human astrocytoma cells. *J Immunol* 159: 4952-4958.

Lieb K, Schaller H, Bauer J, Berger M, Schulze-Osthoff K, Fiebich BL (1998) Substance P and histamine induce interleukin-6 expression in human astrocytoma cells by a mechanism involving protein kinase C and nuclear factor-IL-6. *J Neurochem* 70: 1577-1583.

Lieb K, Ahlvers K, Dancker K, Strobusch S, Reincke M, Feige B, Berger M, Riemann D, Voderholzer U (2002a) Effects of the neuropeptide substance P on sleep, mood, and neuroendocrine measures in healthy young men. *Neuropsychopharmacol* 27: 1041-1049.

Lieb K, Treffurth Y, Berger M, Fiebich BL (2002b): Substance P and affective disorders: new treatment opportunities by NK-1-receptor antagonists? *Neuropsychobiol* 45 (Suppl 1): 2-6.

Lieb K, Herpfer I, Fiebich BL, Berger M (2002c) Substance P-antagonists as a new class of antidepressant drugs. *Dtsch Med Wochenschr* 127: 2563-2565.

Lieb K, Treffurth Y, Hamke M, Akundi RS von Kleinsorgen M, Fiebich BL (In Press) Valproic acid inhibits substance P-induced activation of protein kinase C epsilon and expression of the substance P receptor. *J Neurochem*.

Lieb K, Walden J, Grunze H, Fiebich BL, Berger M, Normann C (Submitted a) Serum level of substance P as a possible predictor of antidepressant response.

Littman BH, Newton FA, Russell IJ (1999) Substance P antagonism in fibromyalgia: a trial with CJ-11974. In: Abstracts from the World Conference on Pain. IASP Press, Seattle, WA, p67.

Manji HK, Lenox RH (1999) Ziskind-Somerfeld Research Award. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. *Biol Psychiatry* 46: 1328-1351.

Martensson B, Nyberg S, Toresson G, Brodin E, Bertilsson L (1989) Fluoxetine treatment of depression. *Acta Psychiatr Scand* 79: 586-596.

Mathe AA, Jousisto-Hanson J, Stenfors C, Theodorsson E (1990) Effect of lithium on tachykinins, calcitonin gene-related peptide, and neuropeptide Y in rat brain. *J Neurosci Res* 26: 233-237.

Mathe AA, Wikner BN, Stenfors C, Theodorsson E (2001) Effects of lithium on neuropeptide Y, neurokinin A and substance P in brain and peripheral tissues of the rat. *Lithium* 5: 241-247.

Maubach KA, Martin K, Chicchi G, Harrison T, Wheeldon A, Swain CJ, Cumberbatch MJ, Rupniak NM, Seabrook GR (2002) Chronic substance P (NK1) receptor antagonist and conventional antidepressant treatment increases burst firing of monoamine neurones in the locus coeruleus. *Neuroscience* 109: 609-617.

McElroy JF, Weidemann KA, Zeller KL, Jones KW, Arneric SP (1999) Acute efficacy of the substance P (NK1) antagonist L-733060 in rat learned helplessness, a chronic animal model of depression. *Soc Neurosci Abstr* 25: 31.15.

Millan MJ, Lejeune F, de Nanteuil G, Gobert A (2001) Selective blockade of neurokinin NK1 receptors facilitates the activity of adrenergic pathways projecting to frontal cortex and dorsal hippocampus in rats. *J Neurochem* 76: 1949-1954.

Navari RM, Reinhardt RR, Gralla RJ, Kris MG, Hesketh PJ, Khojasteh A, Kindler H, Grote TH, Pendergrass K, Grunberg SM, Carides AD, Gertz BJ (1999) Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. *N Engl J Med* 340: 190-195.

Otsuka M, Yoshioka K (1993) Neurotransmitter functions of mammalian tachykinins. *Physiological Reviews* 73: 229-308.

Papp M, Vassout A, Gentsch C (2000) The NK1-receptor antagonist NKP608 has an antidepressant-like effect in the chronic mild stress model of depression in rats. *Behav Brain Res* 115: 19-23.

Pauls J, Bandelow B, Ruther E, Kornhuber J (2000) Polymorphism of the gene of angiotensin converting enzyme: lack of association with mood disorder. *J Neural Transm* 107: 1361-1366.

Pioro EP, Mai JK, Cuellar AC (1990) Distribution of substance P and enkephalin immunoreactive neurons and fibers. In: The human nervous system. Paxinos G (ed) Academic Press, San Diego, pp 1051-1094.

Quartara L, Maggi CA (1998) The tachykinin NK1 receptor. Part II: Distribution and pathophysiological roles. *Neuropeptides* 32: 1-49.

Richardson JD, Vasko MR (2002) Cellular mechanisms of neurogenic inflammation. *J Pharmacol Exp Ther* 302: 839-845.

Rimon R, Le Greves P, Nyberg F, Heikkila L, Salmela L, Terenius L (1984) Elevation of substance P-like peptides in the CSF of psychiatric patients. *Biol Psychiatry* 19: 509-516.

Rupniak NMJ (2002a) Elucidating the antidepressant actions of

substance P (NK1 receptor) antagonists. *Curr Opin Investig Drugs* 3: 257-261.

Rupniak NMJ (2002b) New insights into the antidepressant actions of substance P (NK1 receptor) antagonists. *Can J Physiol Pharmacol* 80: 489-494.

Rupniak NMJ, Hill RG (2000) Opioids and beyond. In: Novel aspects of pain management. Sawynok J, Cowan A (eds) John Wiley Press, New York, pp 135-155.

Rupniak NMJ, Kramer MS (1999) Discovery of the antidepressant and anti-emetic efficacy of substance P receptor (NK1) antagonists. *Trends Pharmacol Sci* 20: 485-490.

Rupniak NMJ, Carlson EC, Harrison T, Oates B, Seward E, Owen S, de Felipe C, Hunt S, Wheeldon A (2000) Pharmacological blockade or genetic deletion of substance P (NK1) receptors attenuates neonatal vocalisation in guinea-pigs and mice. *Neuropharmacology* 39: 1413-1421.

Rupniak NMJ, Carlson EJ, Webb JK, Harrison T, Porsolt RD, Roux S, de Felipe C, Hunt SP, Oates B, Wheeldon A (2001) Comparison of the phenotype of NK1R-/- mice with pharmacological blockade of the substance P (NK1) receptor in assays for antidepressant and anxiolytic drugs. *Behav Pharmacol* 12: 497-508.

Russel IJ (2002) The promise of substance P inhibitors in fibromyalgia. *Rheum Dis Clin N Am* 28: 329-342.

Russell IJ, Orr MD, Littman B, Vipraio GA, Alboukrek D, Michalek JE, Lopez Y, MacKillip F (1994) Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthritis Rheum* 37: 1593-1601.

Santarelli L, Gobbi G, Debs PC, Sibille ET, Blier P, Hen R, Heath MJ (2001) Genetic and pharmacological disruption of neurokinin 1 receptor function decreases anxiety-related behaviors and increases serotonergic function. *Proc Natl Acad Sci U S A* 98: 1912-1917.

Schedlowski M, Fluge T, Richter S, Tewes U, Schmidt RE, Wagner TO (1995) Beta-endorphin, but not substance-P, is increased by acute stress in humans. *Psychoneuroendocrinology* 20: 103-110.

Sergeyev V, Hokfelt T, Hurd Y (1999) Serotonin and substance P co-exist in dorsal raphe neurons of the human brain. *Neuroreport* 10: 3967-3970.

Shirayama Y, Mitsushio H, Takashima M, Ichikawa H, Takahashi K (1996) Reduction of substance P after chronic antidepressants treatment in the striatum, substantia nigra and amygdala of the rat. *Brain Res* 739: 70-78.

Sivam SP, Krause JE, Takeuchi K, Li S, McGinty JF, Hong JS (1989) Lithium increases rat striatal beta- and gamma-preprotachykinin messenger RNAs. *J Pharmacol Exp Ther* 248: 1297-1301.

Snijdelaar DG, Dirksen R, Slappendel R, Crul BJ (2000) Substance P. *Eur J Pain* 4: 121-135.

Stockmeier CA, Shi X, Konick L, Overholser JC, Jurjus G, Meltzer HY, Friedman L, Blier P, Rajkowska G (2002) Neurokinin-1 receptors are decreased in major depressive disorder. *NeuroReport* 13: 1223-1227.

Stout SC, Owens MJ, Nemeroff CB (2001) Neurokinin(1) receptor antagonists as potential antidepressants. *Annu Rev Pharmacol Toxicol* 41: 877-906.

Toresson G, Brodin E, Wahlström A, Bertilsson L (1988) Detection of N-terminally extended substance P, but not of substance P in human cerebrospinal fluid—quantitation with HPLC-RIA. *J Neurochem* 50: 1701-1707.

Van Belle S, Lichinitser MR, Navari RM, Garin AM, Decramer ML, Riviere A, Thant M, Brestan E, Bui B, Eldridge K, De Smet M, Michiels N, Reinhardt RR, Carides AD, Evans JK, Gertz BJ (2002) Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869. *Cancer* 94: 3032-3041.

Vaeroy H, Helle R, Forre O, Kass E, Terenius L (1988) Elevated CSF

levels of substance P and high incidence of Raynaud phenomenon in patients with fibromyalgia: new features for diagnosis. *Pain* 32: 21-26.

Weiss DW, Hirt R, Tarcic N, Berzon Y, Ben-Zur H, Breznitz S, Glaser B, Grover NB, Baras M, O'Dorisio TM (1996) Studies in psychoneuroimmunology: psychological, immunological, and neuroendocrinological parameters in Israeli civilians during and after a period of Scud missile attacks. *Behav Med* 22: 5-14.

A Controlled Study of Psychopathology and Associated Symptoms in Tourette Syndrome

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Summary

Background: Gilles de la Tourette syndrome (GTS) is a neurobehavioural disorder of genetic origin, although the precise inheritance pattern is as yet undetermined. This study was designed to describe symptomatology in GTS subjects. It describes the severity of depressive, anxiety and obsessional symptoms when compared to other samples of GTS patients, matched controls and normative data.

Methods: 87 consecutive GTS clinic referrals (children and adults) were interviewed in 1996 and 1997 using the National Hospital Interview Schedule, the Yale Global Tourette Severity Score, the Diagnostic Confidence Index, Beck Depression Inventory (BDI), Spielberger State-Trait Anxiety Index (STAI) and Leyton Obsessional Inventory (LOI). 52 healthy controls were interviewed using the BDI, STAI and LOI. The clinical status of the subjects was described and ratings of psychopathology were compared with the control group and with normative data. Data were compared with previous data from similar clinic samples.

Results: In this controlled study, GTS subjects scored highly on ratings of depression, state anxiety and obsessionalism when compared with controls and with normative data. Scores in the subjects group were similar to previous findings in clinic samples of people with GTS.

Conclusions: People with GTS who attend clinics have a variety of psychological symptoms that are significantly more severe than controls. Accessory symptoms (e.g. coprophenomena, echophenomena) were also very common in the subject group. Psychological symptoms may occur as part of the disease, a reaction to disability or as a result of ascertainment bias.

Key words: Tourette Syndrome, depression, anxiety, obsessive compulsive disorder, mental health.

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Introduction

The Gilles de la Tourette syndrome (GTS) is a neurobehavioural disorder characterised by multiple motor and one or more vocal tics. Current DSM-IV-TR classification states that tics have to be present for longer than one year and onset has to be before 18 years of age (American Psychiatric Association 2000). The aetiology of this condition is unknown but it is known to be highly familial and genetic influences may well be strong. No single gene has been identified to date, although in a recent full genome scan in GTS sib pairs and their families, regions of interest were identified on chromosomes 4 and 8 (The Tourette Syndrome International Consortium for Genetics 1999). Recent studies have shown the prevalence of GTS to be more than 1% of children (Mason et al. 1998; Kadesj and Gilberg 2000; Hornsey et al. 2001).

The symptoms of GTS possibly occur on a continuum with normal behaviour and some authors have suggested that milder forms of GTS are normal developmental variants (Kurlan 1994).

Many people with GTS have psychological symptoms including depression, anxiety and obsessive compulsive disorder. Some symptoms (such as compulsions) clearly share some phenomenological similarities with tics.

In many studies, obsessive-compulsive (OC) symptoms occur much more commonly than in the general population (Jagger et al. 1982; Montgomery et al. 1982; Nee et al. 1980; Pauls and Leckman 1986). These studies are all either clinic based or (in the case of Pauls and Leckman 1986) the result of an investigation of a large pedigree. In a large, multicentre study by Freeman et al. (2000), obsessive-compulsive behaviours (OCB) were reported in 32% and obsessive-compulsive disorder (OCD) in 27% of people with GTS.

Rates of depression have also been studied in GTS. Robertson et al. (1988) used normative data rather than specific controls. GTS subjects scored a mean of 12.6 on the Beck Depression Inventory (BDI; Beck et al. 1961) compared to the normative mean of 5.0. Chee and Sachdev (1994) studied 50 GTS subjects and found that 18% fulfilled DSM-III-R criteria for depression. Freeman et al. (2000) found co-morbid mood disorder in 20% of people with GTS in an international study of 3500 patients.

To the best of our knowledge, there have only been four controlled studies using standardised measures to rate depression in GTS. In one of the few controlled studies, Comings and Comings (1987) examined 246 GTS patients and 47 controls and found that 23% of GTS subjects had a BDI score over 9 compared to 2% of controls (none of the controls had a BDI score over 10).

Robertson et al. (1993), in one of the other controlled studies, compared 22 subjects with GTS, 19 with major depression and 21 normal controls. In this study of clinic patients, the GTS and depressed groups scored significantly higher on all measures (BDI, Leyton Obsessional Inventory [LOI], Snowdon 1980), Spielberger State-Trait Anxiety Index (STAI; Spielberger et al. 1970) than the control group. The GTS subjects had similar scores on the LOI to depressed subjects but lower scores on STAI and BDI. Robertson et al. (1997) studied 39 consecutive adult clinic patients with GTS and compared them with a group of undergraduates. Subjects scored significantly higher on the BDI, LOI and STAI (both State and Trait components)($p < 0.001$ in all comparisons).

More recent studies including the Tourette International Database Consortium (TICS) have emphasised the importance of co-morbidity in clinic samples with GTS but also suggest the existence of a 'pure tics' GTS group (around 11%) with no co-morbid diagnoses (Freeman et al. 2000). Pauls et al. (1994) interviewed first-degree relatives of probands with GTS and compared them to first-degree relatives of controls and to non-biological first-degree relatives of adopted GTS probands. Comparing rates they found that there was no evidence for genetic association between major depression and GTS.

Our study aimed to look at a large cohort of patients and compare them with both controls and normative data to further elucidate the psychopathological profile of clinic patients with GTS.

Method

Consecutive referrals to the GTS clinics at the National Hospital, Queen Square, London and the Queen Elizabeth Psychiatric Hospital, Birmingham were assessed for suitability over a period of one year. Diagnosis was made using DSM-IV criteria, aided by the use of the National Hospital Interview Schedule (Robertson and Eapen 1996), the Diagnostic Confidence Index (DCI; Robertson et al. 1999) and the Yale Global Tourette Severity Scale (YGTSS; Leckman et al. 1989).

The main inclusion criterion was a DSM-IV diagnosis of Gilles de la Tourette Syndrome (APA 1995) Subjects were excluded if they had co-existing neurological or psychiatric disorders.

Healthy controls were recruited from the staff and students of Birmingham and Aston Universities. Exclusion criteria were the same as for subjects but included tic disorders or OCD.

Assessment

All participants were assessed during a direct interview by both authors (MMR and HR). All subjects completed the NHIS, YGTSS and DCI (see above). Subjects and controls all completed the Beck Depression Inventory (BDI; Beck et al. 1961), the Spielberger State-Trait Anxiety Index (STAI; Spielberger et al. 1970) and the Leyton Obsessional Inventory (LOI; Snowdon 1980).

Analysis

Student's t-test for independent samples was used to compare demographic and psychopathological data between subjects and controls. Significance was set at the 5% level with a two-tailed test. The sex distribution of the GTS subjects vs. controls was compared using χ^2 .

Results

• Description of GTS patients group — see Figure 1

The mean score for patients on the YGTSS (Yale Global Tourette Severity Score) was 28.4. The mean DCI score was 66.14. The mean total motor tic score was 35.2. The mean vocal tic score was 10.47.

Coprolalia was present in 35 patients (42%) and absent in 49 patients (56%). Echolalia was present in 48 patients (55%) and absent in 36 patients (41%). Forty-nine patients (61%) had a family history of obsessive-compulsive behaviours and 31 (39%) did not. There was a family history of tics in 66 patients (83%) and no family

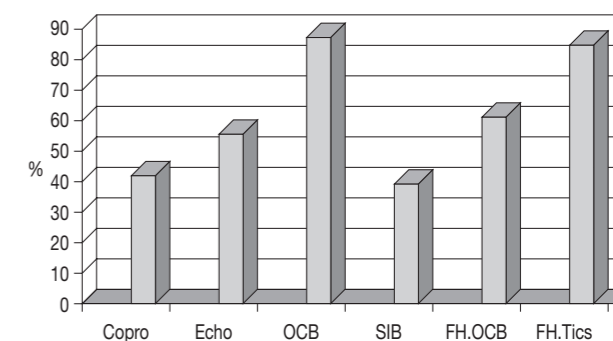


Figure 1 Prevalence of accessory symptoms and family history in 89 cases of Tourette syndrome

Legend

Copro = coprophenomena
Echo = echophenomena
OCB = Obsessive Compulsive behaviour
SIB = Self-injurious behaviour
FH. OCB = Family History of Obsessive Compulsive Behaviour
FH. Tics = Family History of Tics

history in 13 (16.5%). Obsessive-compulsive behaviours were present in 69 patients (87%) and not present in 10 patients (13%). Self-injurious behaviours (SIB) were less common occurring in 33 patients (39%) and not reported in 51 patients (61%).

• Data comparison between patients and controls — see Figure 2

1. *Age.* Mean age of patients was 22.4 years (SD = 11.96). Mean age of controls was 20.2 years (SD = 9.63). These means were not significantly different ($t = 0.85$, $p < 0.397$).

2. *Sex.* The sex distribution of subjects was 69% male vs. 31% female. For controls the distribution was 58% male vs. 42% female. Using Chi-squared test, this was not significantly different ($p < 0.05$).

3. *Leyton Obsessional Inventory (LOI).* There was an expected significant difference in scoring on the LOI. Mean score for patients was 28.05 (SD = 14.17). Mean score for controls was 16.77 (S.D. = 9.72) ($t = 3.696$, $p < 0.0001$).

4. *Beck Depression Inventory.* Scores on the Beck Depression Inventory were also significantly different when patients' mean scores were compared to controls (mean patient score was 11.5 (SD = 8.0) vs. mean control score 4.6 (SD = 3.4) ($t = 4.78$, $p < 0.0001$).

5. *Spielberger State-Trait Anxiety Index (State).* Scores on the STAI (state) were significantly higher in patients when compared to controls (patient mean 49.3 (SD = 11.7) vs. control mean 34.6 (SD 9.71) ($t = 4.96$, $p < 0.0001$).

• Comparison with previous and normative data — see Figure 2

Three previous studies have been conducted using the same selection methodology in the

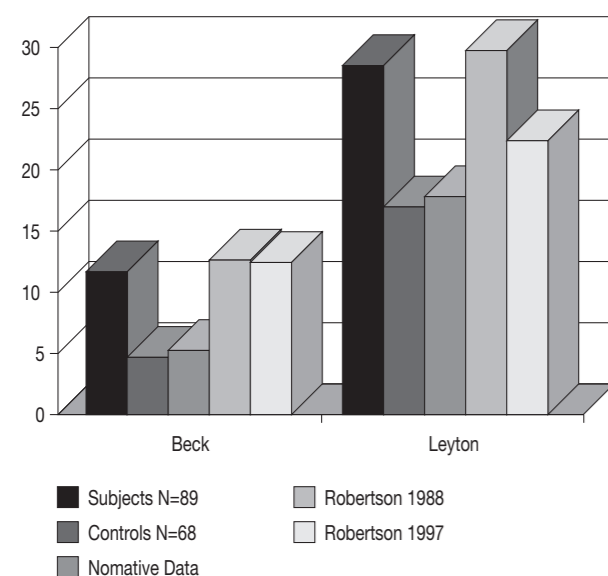


Figure 2
Scores on BDI and LOI in GTS subjects and controls

Beck = Beck Depression Inventory
Leyton = Leyton Obsessional Inventory

same clinic. In our subjects (*vide supra*), the mean score on BDI was 11.51. This compares with three previous studies showing mean BDI scores of 12.6 (Robertson et al. 1988), 12.09 (Robertson et al. 1993) and 12.3 (Robertson et al. 1997). Robertson et al. (1993) also included a group of subjects with depression (N=19). The mean BDI score in this depressed group was 25.32, which was significantly higher. Controls in our study had a mean BDI of 4.6 compared with 2.71 (Robertson et al. 1993), 0.7 (Robertson et al. 1997) and 5.0 for the normative BDI score for controls (Metcalf and Goldman 1965).

Our patients' mean score of 49.3 on the 'state' part of the STAI compares with 54.37 (Robertson et al. 1993), 47.0 (Robertson et al. 1988) and 44.6 (Robertson et al. 1997). Subjects with depression in Robertson et al.'s study (1993) had a mean STAI (state) score of 54.37. The mean control score was 34.55, compared with 29.39 (Robertson et al. 1993), 29.0 (Robertson et al. 1997) and with normative means of 38.1 (Spielberger et al. 1970) and 33.0 (Price and Blackwell 1980).

Discussion

The mean score on the YGTSS measure was 28.4. In the comparable studies, Robertson et al. (1996) examined the efficacy of risperidone in GTS found a mean YGTSS score of 33, and Robertson et al. (1997) found a mean YGTSS score of 26.2. Our data indicate that the symptoms of GTS were of moderate severity, which would be expected given the specialist, tertiary nature of both clinics.

Although a specific score on the DCI was not used to create a cut-off for diagnosis, the index was used as a diagnostic aid. Mean score on this index for subjects was 66.14. This compares with a score of 60 in Robertson et al.'s 1999 study during the development of the instrument in a specialised clinic. This illustrates a high degree of diagnostic certainty in the patients' group.

The mean cumulative motor tic score was 35.2, compared with a mean motor tic score of only 10.3 in the study by Robertson et al. (1988), and the mean cumulative vocal tic score was 10.7, compared with only 4.8 in the same study by Robertson et al. (1988). Both of these sets of data were collected from the same clinic, the only difference being a seven-year time lapse. Reasons for the difference in tic scores include closer questioning in this study, a more detailed National Hospital Interview Schedule and possible changes in the patient group between 1988 and 1995, with the latter patients having more severe forms of the illness.

Coprolalia was present in 42% of the GTS patients. This is on the high end of the range when compared to other clinic populations (the

range being from 4% to 55% but most studies range between 27% and 40%). This may well be owing to the specialist nature of the clinics attracting patients who have more severe symptomatology. Echolalia or echopraxia was present in a relatively high proportion of patients (55%). This compares with 44% in Robertson et al.'s (1988) study. Other studies have reported rates of between 15% and 45% (see Robertson 1989 for review).

OCB's were present in 87% of GTS subjects in this study. This again is on the high end of the range for other clinic-based studies, the range being from 30% – 90% (see Montgomery et al. 1982; Nee et al. 1982; Pauls et al. 1986; Robertson et al. 1988). Freeman et al. (2000) reported 32% OCB alone and 27% OCD alone. Again, our result is on the high end of the range compared to other studies (especially the study of Freeman et al.).

SIB occurred in 39%, which is in line with other studies (range between 30% and 50%). However, Freeman et al. (2000) reported SIB in only 14%.

In this study there was a family history of tics in 83% (anyone in the family had tics). This compares to a figure of 59% from Robertson et al.'s (1988) paper. There was a family history of OCB in 61% of GTS probands. There is no obvious comparison in the literature for this figure.

When this study is viewed in the context of previous studies, the multicentre study of Freeman et al. (2000) stands out for the relatively low levels of coprolalia and SIB (14% prevalence of both, compared with 42% and 39% respectively in our study). Our relatively increased rate of eliciting SIB could be accounted for by our use of detailed questioning (in particular, the use of the NHIS) but it is more difficult to explain the big differences in the rates of coprolalia in this way. Possibly, this represents a transatlantic difference in diagnosis (Freeman et al.'s study predominantly took patients from North America). In addition, our study excluded those people with 'mental impairment' and 23% of Freeman et al.'s sample were reported as having 'specific learning difficulty' (this may also reflect a problem in the use of terminology).

Comparisons between subjects and controls

When comparing the subjects to controls there was a similar distribution of age and sex when the two groups were compared.

GTS subjects score very highly on both subscales of the Leyton Obsessional Inventory. The scores are similar to other studies of subjects with GTS and are significantly higher than control or normative data. Data for controls and normative data are not significantly different from each

other. The links between GTS and obsessive compulsive disorder are established on many levels including phenomenology and neuro-anatomy. These data add further weight to this link, especially in a clinic population.

Scores on the BDI and STAI (State) were also significantly increased. This increase, compared with controls and normative data, was similar to previous studies on similar populations. Anxiety is an important aspect of the psychopathology of GTS, with its own treatment implications. However, it has received relatively scant attention from researchers. Depression in GTS is highly likely to be multifactorial in aetiology (Robertson 2000). Factors include referral bias (Berkson 1946) and adverse experiences as a result of having a disabling neurological condition. Anxiety scores are clearly also high in GTS but to date there are few controlled studies examining this.

The lack of obvious factor clusters explaining the variance in response to the BDI may well be explained by the relatively small numbers in the study completing the BDI.

Conclusions

It is now recognised that GTS is no longer an uncommon illness and it is highly likely to be genetic. Our study, along with others, shows that co-morbidity in GTS is high. This has extremely important implications with regard to the training of health professionals and to the provision of services for people with GTS.

Suggestions for further research could include assessing psychopathology in individuals with mild GTS who are not receiving medical care for their condition, such as mildly affected relatives of clinic GTS probands. Principal component analysis of rating scales such as the BDI or LOI in a larger sample of people with GTS may also be fruitful.

References

- American Psychiatric Association (1995) Diagnostic and Statistical Manual of Mental Disorders – 4th Edition (DSM-IV) American Psychiatric Association, Washington DC.
- American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders-Text Revised (DSM-IV-TR) American Psychiatric Association, Washington DC.
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An Inventory for Measuring Depression. Arch Gen Psych 4: 561-571.
- Berkson J (1946) Limitations of the application of fourfold table analysis to hospital data. Biometrics 2: 45-47.
- Chee KY, Sachdev P (1994) The clinical features of Tourette's disorder: an Australian study using a structured interview schedule. Austr N Z J Psychiatr 28: 213.

Comings BG, Comings DE (1987) A controlled study of Tourette syndrome V: Depression and mania. *Am J Hum Genet* 41: 804-821.

Freeman R D, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P (2000) An International Perspective on Tourette syndrome: selected findings from 3500 individuals in 22 countries. *Dev Med Child Neurol* 42: 436-447.

Hornsey H, Banerjee S, Zeitlin H, Robertson MM (2001) The prevalence of Tourette syndrome in 13-14 year olds in mainstream schools. *J Child Psychol Psychiatry* 8: 1035-1039.

Jagger J, Prusoff BA, Cohen DJ, Kidd KK, Carbonari CM, John K (1982) The epidemiology of Tourette syndrome. A pilot study. *Schizophr Bull* 8: 267-278

Kadesj B, Gillberg C (2000) Tourette's Disorder: Epidemiology and Comorbidity in Primary School Children. *J Am Acad Child Adolesc Psychiatry* 39: 548-555.

Kurlan R (1994) Hypothesis II: Tourette's syndrome is part of a clinical spectrum that includes normal brain development. *Arch Neurol* 51: 1145-1150.

Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz K, Stevenson J, Cohen DJ (1989) The Yale Global Tic Severity Scale. *J Am Acad Child Adolesc Psychiatry* 28: 566-573.

Mason A, Banerjee S, Eapen V, Zeitlin H, Robertson MM (1998) The prevalence of Tourette Syndrome in a mainstream school population. *Dev Med Child Neurol* 40: 292-296.

Metcalf M, Goldman E (1965) Validation of an instrument for measuring depression. *Br J Psychiatry* 111: 240-242.

Montgomery MA, Clayton PJ, Freidhoff AJ (1982) Psychiatric illness in Tourette syndrome patients and first degree relatives. *Adv Neurol* 35: 335-339.

Nee LE, Caine ED, Polinsky RJ, Eldridge R, Ebert MH (1980) Gilles de la Tourette syndrome: Clinical and family study of 50 cases. *Ann Neurol* 7: 41-49.

Pauls DL, Leckman JF (1986) The inheritance of Gilles de la Tourette syndrome and associated behaviours. *N E J M* 315: 993-997.

Pauls DL, Leckman JF, Cohen DJ (1994) Evidence against a genetic relationship between Tourette's syndrome and anxiety, depression, panic and phobic disorders. *Br J Psychiatry* 164: 215-221.

Price KP, Blackwell S (1980) Trait levels of anxiety and psychological responses to stress in migraineurs and normal controls. *J Clin Psychol* 36: 658-660.

Robertson MM (1989) The Gilles de la Tourette Syndrome: the current status. *Br J Psychiatry* 154: 147-169.

Robertson MM (2000) Tourette Syndrome, associated conditions and the complexities of treatment. *Brain* 123: 425-462.

Robertson MM, Eapen V (1996) The National Hospital Interview Schedule for the Assessment of Gilles de la Tourette Syndrome. *Int J Methods Psychiatry Res* 6: 203-226.

Robertson MM, Trimble MR, Lees AJ (1988) The psychopathology of Gilles de la Tourette syndrome: A phenomenological analysis. *Br J Psychiatry* 152: 383-390.

Robertson MM, Channon S, Baker J, Flynn D (1993) The psychopathology of Gilles de la Tourette syndrome: a controlled study. *Br J Psychiatry* 162: 114-117.

Robertson MM, Scull DA, Eapen V, Trimble M (1996) Risperidone in the treatment of Tourette's syndrome—a retrospective case notes study. *J Psychopharmacol* 10: 317-320.

Robertson MM, Banerjee S, Fox Hiley P, Tannock C (1997) Personality Disorder and Psychopathology in Tourette's Syndrome: a controlled study. *Br J Psychiatry* 171: 283-286.

Robertson MM, Banerjee S, Kurlan R, Cohen DL, Leckman JF, Mc

Mahon W, Pauls DL, Sandor P, van der Wetering BJM (1999) The Tourette Syndrome Diagnostic Confidence Index: development and clinical associations. *Neurology* 53: 2108-2112.

Snowdon J (1980) A comparison of written and postbox forms of the Leyton Obsessional Inventory. *Psych Med* 10: 165-170.

Spielberger CD, Gorsuch RL, Lushene RE (1970) Manual for the State-Trait Anxiety Inventory (Self Evaluation Questionnaire). Consulting Psychologists Press, Palo Alto.

The Tourette Syndrome Association International Consortium for Genetics (1999) A complete genome screen in sib pairs affected by Gilles de la Tourette Syndrome. *Am J Hum Genet* 65: 1428-1436.

Association Analysis of Serotonin 2A Receptor Gene T102c Polymorphism and Schizophrenia

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Summary

The serotonin neurotransmitter has been associated with the pathogenesis of mood disorders and schizophrenia. Serotonin receptors genes may therefore be candidate genes for the study of the genetics of these disorders. In this study, patients with schizophrenia (n=235) and controls (n=344) were analysed to determine the correlation between the 5HT_{2A} receptor gene T102C polymorphism and schizophrenia. No association was found between the studied polymorphism and schizophrenia (p=0.854 for alleles and p=0.945 for genotypes). Results were also not significant when analysed by gender (for male p=0.861—allele frequency and p=0.467—genotype frequency, for female p=0.857—allele frequency and p=0.833—genotype frequency). Subgroups with regard to schizophrenia subtypes, age of onset and clinical course of schizophrenia were analysed with negative results.

Key words: serotonin receptor, genetics, polymorphism, schizophrenia.

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Introduction

The hypothesis that serotonin may be implicated in the pathophysiology of schizophrenia was first made in 1954, following observations that the hallucinogen LSD could act as a potent serotonin antagonist, causing hallucinations (Wooley and Shaw 1954). Furthermore, serotonin has become of great interest in the search for the causes of the pathology of schizophrenia due to observations that many atypical antipsychotics are not only dopamine receptor antagonists but also have potent serotonin-related activities. This has been further supported by the finding that clozapine and risperidone have 5HT₂-blocking properties (Meltzer et al. 1989; Meltzer 1991; Leysen et al. 1993). The effects of selective serotonin 2A receptor antagonists on the negative symptoms of schizophrenia suggest that the serotonin 2A receptor might be involved in the pathophysiology of schizophrenia (Meltzer 1999). The gene that encodes the serotonin 2A receptor has been cloned and localized to chromosome 13q14-q21 (Hsieh et al. 1990; Saltzman et al. 1991). The human 5-HT_{2A}-receptor gene consists of three exons (Chen K et al. 1992), and several polymorphisms were described:

- a silent polymorphism – T/C substitution at position 102, results in two alleles: allele 1 (T) allele 2 (C) (Warren et al. 1993),
- a silent polymorphism – C/T substitution at position 516 (Arranz et al. 1995),
- a structural polymorphism – His/452/Tyr substitution (Erdmann et al. 1996),
- a structural polymorphism – Thr/25/Asn substitution (Erdmann et al. 1996),
- a single nucleotide polymorphism G to A substitution at position -1438 of the 5HT_{2A} promoter region (which is in linkage disequilibrium with the 102T/C polymorphism) (Spurlock et al. 1998).

T102C polymorphism of the 5-HT_{2A} gene is the subject of this study. The conclusions of existing research on this polymorphism are contradictory. Some studies describe an association of schizophrenia with allele C or allele T, but this was not confirmed by others. It has been suggested that different 5HT_{2A} gene polymorphisms may influence response to neuroleptic treatment but not necessarily directly be associated with the susceptibility to schizo-

phrenia. However, the conclusions of these studies do not all agree (Arranz et al. 1995; Arranz et al. 1998; Joober et al. 1999; Yu et al. 2001; Masellis et al. 1998; Lin et al. 1999; Malhotra et al. 1996; Nimgaonkar et al. 1996; Lane et al. 2002).

Polymorphisms of the 5HT_{2A} gene were also reported to be associated with susceptibility to tardive dyskinesia in schizophrenic patients, but results are equivocal (Basile et al. 2001; Tan et al. 2001; Segman et al. 2001).

Subjects and Methods

• Subjects

The study was performed in 235 patients with schizophrenia (141 male, 94 female), mean age 30.6 years (SD=10.5). The mean age at onset was 22.9 years (SD=5.8), the mean illness duration was 7.4 years (SD=7.9). There were 224 patients with paranoid, nine with residual and two with undifferentiated schizophrenia subtype. Patients were recruited from inpatients at the Department of Adult Psychiatry, University of Medical Sciences in Poznan. Consensus diagnosis by two psychiatrists using ICD-10 and DSM-IV classification was made for each patient using SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders) (First et al. 1996). In the group of 139 patients (duration of illness at least one year) to DSM-IV criteria allowed the characteristic course of symptoms of schizophrenia to be specified over time. According to SCID, nine types of course of schizophrenia were specified: episodic, with interepisode residual symptoms, with prominent negative symptoms (n=11); episodic with interepisode residual symptoms (n=36); episodic with no interepisode residual symptoms (n=29); continuous, with prominent negative symptoms (n=31); continuous (n=25); single episode, with prominent negative symptoms (n=1); single episode, in partial remission (n=3); single episode, in full remission (n=3); other or unspecified pattern (n=0).

A control group of 344 subjects (137 male, 207 female) were recruited from blood donors. They were not psychiatrically screened. The mean age of this control group was 41 years (SD=11). All individuals participating in the study were of

Polish origin. The project was approved by the local ethics committee.

• Method of genotyping

Genomic DNA was extracted from anticoagulated venous blood samples using a salting-out method. Genotyping was performed as previously described (Warren et al. 1993) using the primers 5-HT2AR-1 (5'-AGC AGA AAC TAT AAC CTG TT-3') and 5-HT2AR-2 (5'-CAA GTG ACA TCA GGA AAT AG-3') (Du et al. 2000). PCR amplification of the region of the 5HT_{2A} gene containing the T102C polymorphic site produced a 342 base-pair (bp) fragment. This was digested by HpaII restriction endonuclease. The uncut product corresponds to allele 1 (T); the digested product (fragments sizes: 216 bp and 126 bp) corresponds to allele 2 (C).

• Statistical analyses

The Pearson's chi-square (χ^2) test and Fisher's exact test were applied to test differences in the genotypic and allelic distribution respectively between the groups of schizophrenic patients and controls. Calculations were performed using the computer programme SPSS version 10. A two-tailed type I error rate of 5% was chosen for analysis. Power analysis was performed using an on-line internet service provided by the UCLA Department of Statistics (<http://ebook.stat.ucla.edu/calculators/powercalc/binomial/case-control/b-case-control-power.php>).

Results

The genotype distribution was in Hardy-Weinberg equilibrium for the patients with schizophrenia $p=0.75$, and for controls $p=0.92$.

Comparing the group of schizophrenic patients and controls we did not find any differences in the frequency of genotypes ($p=0.945$; see Table 1). Analysis of genotypes by gender also did not show significant differences either for males ($p=0.467$, $\chi^2=1.524$, $df=2$) or females ($p=0.833$, $\chi^2=0.366$, $df=2$). A comparison of the frequency of alleles in the whole group of schizophrenic patients versus controls was not statistically significant ($p=0.854$; see Table 1). Analysis of alleles by gender also did not reveal any significant differences on comparison with the

Table 1

Genotype distribution and allele frequencies of serotonin 5HT_{2A} receptor gene for patients with schizophrenia and the control group

	Geno-type T/T n (%)	Geno-type T/C n (%)	Geno-type C/C n (%)	TOTAL Geno- types n (%)	Allele T n (%)	Allele C n (%)	TOTAL Alleles n (%)
schizophrenia	85 36.2%	115 48.9%	35 14.9%	235 100%	285 60.6%	185 39.4%	470 100%
controls	129 37.5%	164 47.7%	51 14.8%	344 100%	422 61.3%	266 38.7%	688 100%

Difference schizophrenia versus controls — $\chi^2 = 0.113$ $df=2$ $p=0.945$ for genotypes, $p=0.854$ for alleles

control subjects, males ($p=0.861$), females ($p=0.857$). A separate analysis was performed on the subgroup of patients with the paranoid subtype of schizophrenia, the results of which were also being not significant for genotypes ($p=0.945$, $\chi^2=0.114$, $df=2$ for both genders, $p=0.376$, $\chi^2=1.958$, $df=2$ for males, and $p=0.769$, $\chi^2=0.525$, $df=2$ for females) or alleles ($p=0.950$ for both genders, $p=1$ for males, and $p=0.786$ for females).

A subgroup of patients ($n=37$) with early onset (before the age of 18 years) was compared to controls – without significant differences ($p=1$ for alleles and $p=0.977$, $\chi^2=0.047$, $df=2$ for genotypes). Another subgroup of patients ($n=190$) with onset after the age of 18 years was similarly analysed – without significant differences ($p=0.896$ for alleles and $p=0.957$, $\chi^2=0.088$, $df=2$ for genotypes). Patients with early onset were also compared to the group with onset after 18 years, again without significant differences ($p=0.897$ for alleles and $p=0.974$, $\chi^2=0.052$, $df=2$ for genotypes). For eight patients the age at onset was unknown.

A separate analysis of subgroups of patients ($n=139$) divided according to the clinical course of schizophrenia was performed. The allele and genotype frequency did not differ significantly between these groups (for alleles $p=0.219$, $\chi^2=9.491$, $df=7$, for genotypes $p=0.279$, $\chi^2=16.588$, $df=14$).

The sample had a power of 66% for a relative risk of 1.5 and 90% for a relative risk of 1.75.

Discussion

We did not confirm an association between the studied polymorphism of the 5HT_{2A} receptor gene and schizophrenia in either the entire sample studied or when subgroups were analysed. Our results concur with those of Nimgaonkar et al. (1996), Hawi et al. (1997), Verga et al. (1997), Chen et al. (1997), Shinkai et al. (1998), He et al. (1999), Kim et al. (1999), Lin et al. (1999), Virgos et al. (2001), Semwal et al. (2001) and Chen RY et al. (2001), all of whom also did not confirm the association between the T/C 102 polymorphism of the serotonin 2A receptor gene and schizophrenia in case-control and/or family-based studies. However, positive results were obtained according to the studied polymorphism. Inayama et al. (1996) found a positive association between genotype 2/2 and allele 2 of T102C polymorphism and schizophrenia; Erdmann et al. (1996) also found an association with allele 2. Williams et al. (1996) confirmed those results in a multicentre study (for allele 2 and combined group of 1/2 and 2/2 genotypes). Spurlock et al. (1998) demonstrated the association between the allele 2 of T102C polymorphism in the 5HT_{2A} gene and schizophrenia using the family based association test.

Tay et al. (1997) reported an association with allele 1. Golimbet et al. (2000) observed an association with the genotype 2/2 in patients with schizophrenia and schizophrenia spectrum disorders.

We cannot directly explain the observed differences in allele frequencies (of approximately 10-15%) between our study and other European studies concerning this polymorphism. However, results from studies of the dopamine transporter gene by Kang et al. (1999) and the catechol-O-methyltransferase gene by Palmatier et al. (1999) indicate that differences in allele frequencies within European populations are sometimes in the range of 10-15%. We are unaware of any other studies of 5HT_{2A} polymorphism in a Polish population.

Several reasons may explain why no association were found in this study: sampling from different ethnic groups, sizes of the groups, specific subgroups of patients. Positive associations obtained by some researchers may therefore reflect an effect present in only subgroup of patients. Although this polymorphism does not cause an amino acid substitution in the receptor protein, it is in a very strong linkage disequilibrium with -1438 G/A promoter polymorphism (Spurlock et al. 1998) of at least potentially functional significance.

Recent studies on the 5HT_{2A} gene expression in the human cerebellum and prefrontal cortex suggest that some alterations are present in patients with schizophrenia (Hernandez and Sokolov 2000; Eastwood et al. 2001). However there is no consensus whether the genetic polymorphisms of the 5HT_{2A} receptor are responsible for such differences in gene expression (Kouzmenko et al. 1999; Polesskaya and Sokolov 2002).

References

- Arranz M, Collier D, Sodhi M, Ball D, Roberts G, Price J, Sham P, Kerwin R (1995) Association between clozapine response and allelic variation in 5-HT_{2A} receptor gene. *Lancet* 346: 281-282.
- Arranz MJ, Munro J, Owen MJ, Spurlock G, Sham PC, Zhao J, Kirov G, Collier DA, Kerwin RW (1998) Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT_{2A} receptor gene and response to clozapine. *Mol Psychiatry* 3: 61-66.
- Basile VS, Ozdemir V, Masellis M, Meltzer HY, Lieberman JA, Potkin SG, Macciardi FM, Petronis A, Kennedy JL (2001) Lack of association between serotonin-2A receptor gene (HTR2A) polymorphisms and tardive dyskinesia in schizophrenia. *Mol Psychiatry* 6: 230-234.
- Chen K, Yang W, Grimsby J, Shih JC (1992) The human 5HT₂ receptor is encoded by a multiple intron-exon gene. *Mol Brain Res* 14: 20-26.
- Chen CH, Lee YR, Wei FC, Koong FJ, Hwu HG, Hsiao KJ (1997) Lack of allelic association between 102T/C polymorphism of serotonin

- receptor type 2A gene and schizophrenia in Chinese. *Psychiatry Genet* 7: 35-38.
- Chen RY, Sham P, Chen EY, Li T, Cheung EF, Hui TC, Kwok CL, Lieh-Mak F, Zhao JH, Collier D, Murray R (2001) No association between T102C polymorphism of serotonin-2A receptor gene and clinical phenotypes of Chinese schizophrenic patients. *Psychiatry Res* 105: 175-185.
- Du L, Bakish D, Lapierre YD, Ravindran AV, Hrdina PD (2000) Association of polymorphism of serotonin 2A receptor gene with suicidal ideation in major depressive disorder. *Am J Med Genet* 96: 56-60.
- Eastwood SL, Burnet PW, Gittins R, Baker K, Harrison PJ (2001) Expression of serotonin 5-HT(2A) receptors in the human cerebellum and alterations in schizophrenia. *Synapse* 42: 104-114.
- Erdmann J, Shimron-Abarbanell D, Rietschel M, Albus M, Maier W, Korner J, Bondy B, Chen K, Shih JC, Knapp M, Propping P, Nothen MM (1996) Systematic screening for mutations in the human serotonin 2A (5-HT2A) receptor gene: identification of two naturally occurring receptor variants and association analysis in schizophrenia. *Hum Genet* 97: 614-619.
- First MB, Spitzer RL, Gibbon M, Williams J (1996): Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). American Psychiatric Press Inc, Washington, D.C.
- Golimbet VE, Manandian KK, Abramova LI, Orlova VA, Kaleda VG, Oleichik IV, Iurov IuB, Trubnikov VI (2000) [Serotonin receptor gene allele polymorphism (5HT2A) and clinical pathogenetic characteristics in patients with schizophrenia and schizophrenia spectrum disorders] [Article in Russian] *Zh Nevrol Psikhiatr Im S S Korsakova* 100: 36-39.
- Hawi Z, Myakishev MV, Straub RE, O'Neil A, Kendler KS, Walsh D, Gill M (1997) No association or linkage between the 5HT2A/T102C polymorphism and schizophrenia in Irish families. *Am J Med Genet* 74: 370-373.
- He L, Li T, Melville C, Liu S, Feng GY, Gu NF, Fox H, Shaw D, Breen G, Liu X, Sham P, Brown J, Collier D, St.Clair D (1999) 102 T/C polymorphism of serotonin receptor type 2A gene is not associated with schizophrenia in either Chinese or British populations. *Am J Med Gen* 88: 95-98.
- Hernandez I, Sokolov BP (2000) Abnormalities in 5-HT2A receptor mRNA expression in frontal cortex of chronic elderly schizophrenics with varying histories of neuroleptic treatment. *J Neurosci Res* 59: 218-225.
- Hsieh CL, Bowcock AM, Farrer LA, Hebert JM, Huang KN, Cavalli-Sforza LL, Julius D, Francke U (1990) The serotonin receptor subtype 2 locus 5HT2 is on human chromosome 13 near genes for esterase D and retinoblastoma and on mouse chromosome 14. *Somat Cell Mol Genet* 16: 567-574.
- Inayama Y, Yoneda H, Sakai T, Ishida T, Nonomura Y, Kono Y, Takahata R, Koh J, Sakai J, Takai A, Inada Y, Asaba H (1996) Positive association between a DNA sequence variant in the serotonin 2A receptor gene and schizophrenia. *Am J Med Genet* 67: 103-105.
- Joober R, Benkelfat C, Brisebois K, Toulouse A, Turecki G, Lal S, Bloom D, Labelle A, Lalonde P, Fortin D, Alda M, Palmour R, Rouleau GA (1999) T102C polymorphism in the 5HT2A gene and schizophrenia: relation to phenotype and drug response variability. *J Psychiatry Neurosci* 24(2): 141-146.
- Kang AM, Palmatier MA, Kidd KK (1999) Global variation of a 40-bp VNTR in the 3'-untranslated region of the dopamine transporter gene (SLC6A3). *Biol Psychiatry* 46: 151-160.
- Kim YK, Lee MS, Kwak DI (1999) No association between schizophrenia and serotonin receptor type 2A gene in Korea. *Psychiatr Genet* 9: 47-49.
- Kouzmenko AP, Scaffidi A, Pereira AM, Hayes WL, Copolov DL, Dean B (1999) No correlation between A(-1438)G polymorphism in 5-HT2A receptor gene promoter and the density of frontal cortical 5-HT2A receptors in schizophrenia. *Hum Hered* 49: 103-105.
- Lane HY, Chang YC, Chiu CC, Chen ML, Hsieh MH, Chang WH (2002) Association of risperidone treatment response with a polymorphism in the 5-HT(2A) receptor gene. *Am J Psychiatry* 159: 1593-1595.
- Leysen JE, Janssen PM, Schotte A, Luyten WH, Megens AA (1993) Interaction of antipsychotic drugs with neurotransmitter receptor sites in vitro and in vivo in relation to pharmacological and clinical effects: role of 5HT2 receptors. *Psychopharmacology (Berl)* 112(Suppl 1): S40-S54.
- Lin CH, Tsai SJ, Yu YW, Song HL, Tu PC, Sim CB, Hsu CP, Yang KH, Hong CJ (1999) No evidence for association of serotonin-2A receptor variant (102T/C) with schizophrenia or clozapine response in a Chinese population. *Neuroreport* 10: 57-60.
- Malhotra AK, Goldman D, Ozaki N, Breier A, Buchanan R, Pickar D (1996) Lack of association between polymorphisms in the 5-HT2A receptor gene and the antipsychotic response to clozapine. *Am J Psychiatry* 153: 1092-1094.
- Masellis M, Basile V, Meltzer HY, Lieberman JA, Sevy S, Macciardi FM, Cola P, Howard A, Badri F, Nothen MM, Kalow W, Kennedy JL (1998) Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. *Neuropsychopharmacology* 19: 123-132.
- Meltzer HY (1991) The mechanism of action of novel antipsychotic drugs. *Schizophr Bull* 17: 263-287.
- Meltzer HY (1999) The role of serotonin in antipsychotic drug action. *Neuropsychopharmacology* Aug 21(Suppl 2): 106S-115S.
- Meltzer HY, Bastani B, Young Kwon K, Ramirez LF, Burnett S, Sharpe J (1989) A prospective study of clozapine in treatment resistant schizophrenic patients. *Psychopharmacology* 99: 68-72.
- Nimgaonkar VL, Zhang XR, Brar JS, DeLeo M, Ganguli R (1996) 5HT2 receptor gene locus: association with schizophrenia or treatment response not detected. *Psychiatr Genet* 6: 23-27.
- Palmatier MA, Kang AM, Kidd KK (1999) Global variation in the frequencies of functionally different catechol-O-methyltransferase alleles. *Biol Psychiatry* 46(4): 557-567.
- Polesskaya OO, Sokolov BP (2002) Differential expression of the 'C' and 'T' alleles of the 5-HT2A receptor gene in the temporal cortex of normal individuals and schizophrenics. *J Neurosci Res* 67: 812-822.
- Saltzman AG, Morse B, Whitman MM, Ivanshchenko Y, Jaye M, Felder S (1991) Cloning of the human serotonin 5-HT2 and 5-HT1C receptor subtypes. *Biochem Biophys Res Commun* 181: 1469-1478.
- Segman RH, Heresco-Levy U, Finkel B, Goltser T, Shalem R, Schlafman M, Dorevitch A, Yakir A, Greenberg D, Lerner A, Lerer B (2001) Association between the serotonin 2A receptor gene and tardive dyskinesia in chronic schizophrenia. *Mol Psychiatry* 6: 225-229.
- Semwal P, Prasad S, Bhatia T, Deshpande SN, Wood J, Nimgaonkar VL, Thelma BK (2001) Family-based association studies of monoaminergic gene polymorphisms among North Indians with schizophrenia. *Mol Psychiatry* 6: 220-224.
- Shinkai T, Ohmori O, Kojima H, Terao T, Suzuki T, Abe K (1998) Negative association between T102C polymorphism of the 5-HT2a receptor gene and schizophrenia in Japan. *Hum Hered* 48: 212-215.
- Spurlock G, Heils A, Holmans P, Williams J, D'Souza UM, Cardno A, Murphy KC, Jones L, Buckland PR, McGuffin P, Lesch KP, Owen MJ (1998) A family based association study of T102C polymorphism in 5HT2A and schizophrenia plus identification of new polymorphisms in the promoter. *Mol Psychiatry* 3: 42-49.
- Tan EC, Chong SA, Mahendran R, Dong F, Tan CH (2001) Susceptibility to neuroleptic-induced tardive dyskinesia and the T102C polymorphism in the serotonin type 2A receptor. *Biol Psychiatry* 50: 144-147.
- Tay AH, Lim LC, Lee WL, Wong KE, Wong LY, Tsoi WF (1997) Association between allele 1 of T102C polymorphism, 5-hydroxytryptamine 2a receptor gene and schizophrenia in Chinese males in Singapore. *Hum Hered* 47: 298-300.
- Verga M, Macciardi F, Cohen S, Pedrini S, Smeraldi E (1997) No association between schizophrenia and the serotonin receptor 5HT2A in an Italian population. *Am J Med Gen* 74: 21-25.
- Virgos C, Martorell L, Valero J, Figuera L, Civeira F, Joven J, Labad A, Vilella E (2001) Association study of schizophrenia with polymorphisms at six candidate genes. *Schizophr Res* 49: 65-71.
- Warren JT Jr, Peacock ML, Rodriguez LC, Fink JK (1993) An MspI polymorphism in the human serotonin receptor gene (HTR2): detection by DGGE and RFLP analysis. *Hum Mol Genet* 2: 338.
- Williams J, Spurlock G, McGuffin P, Mallet J, Nothen MM, Gill M, Aschauer H, Nylander PO, Macciardi F, Owen MJ (1996) Association between schizophrenia and T102C polymorphism of the 5-hydroxytryptamine type 2a-receptor gene. *The Lancet* 347: 1294-1296.
- Wooley DW, Shaw E (1954) A biochemical and pharmacological suggestion about certain mental disorders. *Proc Natl Acad Sci USA* 40: 228-231.
- Yu YW, Tsai SJ, Yang KH, Lin CH, Chen MC, Hong CJ (2001) Evidence for an association between polymorphism in the serotonin-2A receptor variant (102T/C) and increment of N100 amplitude in schizophrenics treated with clozapine. *Neuropsychobiology* 43: 79-82.

Antidepressant Drugs in the Elderly — Rôle of the Cytochrome P450 2D6

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Summary

Depression, the most common mental health problem of the elderly, is often under-diagnosed and under-treated. As patients age, antidepressant pharmacological treatment becomes more complicated due to an increased risk of adverse drug events. These risks are associated with age-related physiological changes and individual variability in drug metabolism related to several factors, the most frequent of which is polymedication as a result of coexisting chronic illnesses.

Comedications induce drug interactions that depend on the patient's metabolic capacity, linked to the genetically determined cytochrome P450 enzyme (CYP450) function. The effect of some isoenzyme polymorphisms on the pharmacokinetics of many antidepressants and other psychotropic drugs is well characterized.

The author approaches successively the notions of the cytochrome P450 (2D6), its role in drug biotransformation, and the importance of knowing its substrates, inhibitors and inducers in order to predict drug interactions. The clinical significance of this notion, and the help that could be given by genotyping, and phenotyping are also explained. The author's experience on the relationship between drug side effects and patient metabolic status, and on the antidepressant interactions with fluoxetine, fluvoxamine and citalopram, is given in order to rationalize and individualize antidepressant choice in elderly.

Key words: antidepressants, elderly, polymorphic cytochrome P450 2D6, drug interactions.

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Introduction

Depression is the most common mental health problem of the elderly (Cole 2000; Baldwin 2000; Gareri et al. 2000). Moreover, it is often under-diagnosed and under-treated (Katona 2000; Maletta et al. 2000; Rojas-Fernandez et al. 1999). Estimates of the prevalence of geriatric depression vary among studies, from up to 20% (Butler and Lewis 1995), to 4.4% in women and 2.7% in men (Steffens et al. 2000). Among older subjects with current major depression, antidepressant drugs are typically under-utilised (Gurvich and Cunningham 2000), and Steffens et al. found that only 35.7% were taking an antidepressant (Steffens et al. 2000). The intensity of treatment was very low with a poor outcome (Unutzer et al. 2000). Moreover, benzodiazepines may be mis-prescribed for treatment of depressive symptoms (Wilson et al. 1999).

As patients age, pharmacological treatment of depression becomes more complicated due to an increased risk of adverse drug events (Gurwitz et al. 2000). These risks are associated with age-related physiological changes such as decreased kidney or liver capacity and an increased cerebral vulnerability. In addition to these physiological changes, individual variability in drug metabolism, mainly related to polymedication (de Mendonça Lima CA et al. 2000) but also to several other factors such as genetic factors, concurrent diseases and diet (frequent denutrition), may play a role. Late-life depression often coexists with chronic illnesses such as heart disease, diabetes, Parkinson's disease, etc. Consequently, the required polymedication induces potential risks for patients, mainly linked to pharmacokinetic drug interactions with pharmacodynamic consequences. These may lead to drug side effects, and drug compliance is mainly linked to the good clinical tolerance of drugs (Turnheim 2000).

These drug interactions depend on the patient's metabolic capacity linked to the cytochrome P450 enzyme (CYP450) function, which is genetically determined. Genetic factors have indeed long been known to cause inter-individual differences in pharmacokinetics and therapeutic and adverse effects of antidepressants (Alexanderson et al. 1969; Hammer and Sjöqvist 1967). Among the CYP450, two of them are now well known, CYP2D6 and CYP2C19. The effect of their genetic polymorphism (Meyer and Zanger 1997) on the pharmacokinetics of many antidepressants and other psychotropic drugs is well characterized.

Thus, choosing an appropriate psychotropic agent requires a thorough knowledge of these cytochromes, which affect drug metabolism in the liver. "Indeed understanding the P450 system is half the battle in reducing drug interaction risks" and their clinical consequences (Cadieux 1999).

CYP P450 and drug biotransformation

Metabolic drug elimination is normally a multi-step process mainly involving the hepatic cytochrome P450 system, some of these isoenzymes being characterized by a genetic polymorphism. CYP2D6 human polymorphism is of pharmacokinetic interest for at least 30 drugs, including many antidepressants and other psychotropic drugs. It is associated with inter-individual differences in drug metabolism, drug efficacy and toxicity. CYP2D6 polymorphism results from the combination of wild and / or mutant alleles in the gene. The wild allele possesses normal metabolic activity. Some mutant alleles are characterized by a decreased metabolic capacity, some others are inactive. The combination of two different alleles determines the gene metabolic capacity.

Genetic polymorphism results in poor, intermediate, extensive and ultrarapid metabolisers (PMs, IMs, EMs, UMs, respectively). This was discovered in the 1970s (Mahgoub et al. 1977) and since then the allele frequency has been found to differ between different populations (Bertilsson 1995; Kalow and Bertilsson 1994), which should induce interethnic differences in the modality of many drug prescriptions.

Poor metabolisers of CYP2D6 substrates, whose gene results from the combination of two inactive mutant alleles such as *3, 4*, 5*, 6*, 7*, 8*, 16*, are devoid of CYP2D6 metabolic capacity. These patients may suffer from drug side effects even at usual drug dosages due to delayed drug elimination resulting in a drug accumulation in blood and other tissues. However, in these patients there is no risk of competitive drug interactions at this level. Controversely ultrarapid metabolisers, carriers of CYP2D6 gene duplications (Johansson et al. 1993), may be subject to drug underdosage and therapeutic inefficacy (Bertilsson et al. 1997; Brosen and Gram 1989) when taking normal drug doses. The usual dosage of drugs was determined with extensive metabolisers with two active (wild) alleles (such as 1*, 2*, 9*, 10*, 17*), the more frequent genotype in Caucasian populations. Studies comparing EMs and PMs allow intermediate metabolisers to be distinguished, heterogeneous carriers of one active and one deficient or inactive allele, or carriers of two deficient alleles (Raimundo et al. 2000). The metabolic capacity of IMs is between that of EMs and PMs.

Interactions between drugs that are metabolised mainly via the same pathway may be expected

with EMs and more frequently with IMs, since the metabolic capacity of CYP2D6 is saturable. This results in drug overdosage and increased drug toxicity. Moreover, recent data suggest that the risk of drug interaction may depend on the allelic constitution of the genes of IM patients. It could be higher when the intermediate genotype is a result of the combination of two mutant alleles, both possessing either a decreased or no metabolic capacity. In contrast, this risk could be less frequent if the gene is the result of an association between a wild allele (with extensive capacity) and a mutant allele with reduced activity (Haffen et al. 1999b). Intermediate metabolisers may perhaps be considered as a very heterogeneous population with differing metabolic capacities.

For the above mentioned reasons, dose regimens should take drug metabolic capacity into account, especially in elderly people receiving comedications. However, not all drugs use the CYP2D6 metabolic pathway. Therefore, if knowledge of the drug metabolic activity of patient may be useful, it is necessary to know the substrates, inhibitors and inducers of this isoenzyme to predict clinically significant drug interactions.

CYP2D6 and substrates, inhibitors and inducers

The list of drugs that are metabolised by the CYP2D6 pathway is constantly being revised. However, some generalisations can be made. A variety of psychotropic drugs such as antidepressants and neuroleptics are metabolised by CYP2D6 or are inhibitors of this isoenzyme. Among antidepressants, tricyclic and second generation antidepressants are all metabolised by the CYP2D6 pathway. The treatment of mood disorders sometimes necessitates administration of neuroleptics or new antipsychotics. Of these, haloperidol, phenothiazines, thioridazine, risperidone and olanzapine are known to have CYP2D6 affinity. However, due to the frequency of illnesses other than psychiatric ones in the elderly, other drugs are also frequently administered. The main ones using the CYP2D6 metabolic pathway are antiarrhythmics, betablockers, morphine derivatives and some other analgics, tramadol and dextropropoxyphene.

Clinical significance

Due to frequent comedication, saturation of CYP2D6 metabolic activity may induce overdosage, drug side effects, poor drug compliance and therapeutic failure. The clinical implications may vary according to the genotype and phenotype (Bertilsson et al. 1997). As mentioned above, ultrarapid metabolisers, with three or more active alleles, may have extremely low drug plasma levels, which may lead to therapeutic failure or delayed response. Conversely,

intermediate and poor metabolisers have a lower degree of metabolism than extensive metabolisers. This can lead to an accumulation of the drug and may result in concentration-dependent side effects and a poor drug observance, as well as therapeutic failure.

However, the clinical significance of drug polymorphism depends on a variety of factors. The therapeutic index of the administered drugs seems to be one of the main factors, together with the existence or non-existence of active metabolites of the prescribed drug. For example, a poor CYP2D6 metaboliser who is administered paroxetine will have higher drug plasma levels than an extensive metaboliser, but this would be of little consequence due to both the broad therapeutic range, the safety profile of paroxetine and the lack of an active metabolite. However, tricyclic antidepressants have a narrow therapeutic index and active metabolites. Consequently, poor metabolisers will have a parent drug accumulation with concentration-dependent adverse effects, and a lack of active metabolites interacting with other monoamines than the parent drug.

Genotype and phenotype

The CYP2D6 polymorphism can be distinguished by either genotyping or phenotyping methods. Although genotypes seem not to be modified by age, Yamada et al. (1998) reported that the genetically determined metabolic capacity may vary due to many variation factors. First, dosage adjustments based only on the genotype of CYP2D6 are complicated by the presence of active metabolites that are also metabolised. Secondly, several factors that are often present in the elderly, such as drug interactions, reduced liver function and kidney elimination, and poor diet may modify the biotransformation and bioavailability of drugs (Coutts and Urchuk 1999). For this reason, it may be useful to complete the genotype information by a phenotype, which reflects "the actual metabolic capacity". This information allows the drug dosage to be optimally adjusted, in addition to therapeutic drug monitoring (Dahl and Sjöqvist 2000). It is also possible to use the dose recommendations for antidepressants that were calculated or extrapolated for each genotype by Kirchheiner et al. (2001).

Our experience on the relationship between drug side effects and metabolic status

Detection of drug side effect risk factors is interesting for the clinician, mainly to avoid a treatment non-compliance and to increase the percentage of good therapeutic responses. We worked on the extrapyramidal side effects (EPSE) of antidepressants that were mainly reported with Selective Serotonin Reuptake Inhibitors (for

materials and methods, see Vandell et al. 1999). In a group of 65 inpatients receiving antidepressants we observed two subgroups: one consisting of 22 patients suffering from EPSE, and another of 43 patients without drug side effects. In the first group, 45% of the patients were PMs, whereas in the second one only 14.3% had the same phenotype. Concerning the genotypes we observed that the percentage of functional alleles (with extensive metabolic capacity) was higher in the second group, whereas the percentage of nonfunctional alleles (without metabolic activity) was higher in the first group ($p < 0.05$).

Antidepressant choice in the elderly

Second generation antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Noradrenaline Reuptake Inhibitors (SNRIs) and Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs) are frequently recommended and chosen as a first line treatment for depression in elderly patients (Solai 2001). They are easy to use due to the fact that, in contrast to tricyclic antidepressants, SSRI dosage adjustments appear to be unnecessary in elderly depressed patients. They possess some advantages such as fewer anticholinergic effects and a fairly safe cardiovascular profile (Strik et al. 1998). Moreover they are associated with a much lower incidence of fatal toxicity than tricyclics (Leonard 1992). But as SSRIs, all of them have a number of potential adverse effects including falls, hyponatremia, weight loss and drug interactions (Woo and Smythe 1997). However, significantly fewer SSRI-treated than TCA-treated patients dropped out of comparative studies due to side effects (Menting et al. 1996). Studies that have examined the comparative efficacy and safety of SSRIs and tricyclic antidepressants suggest that there are few advantages for one over the other (Herrmann 2000).

However, in clinical practice, the physician often chooses SSRIs as the first line therapy. But as Herrmann said: this choice induces "obvious benefits but unappreciated risks" (Herrmann 2000). It is indeed recommended to consider drug interactions carefully.

Some SSRIs potentially inhibit CYP2D6; in order of decreasing potency these are paroxetine, norfluoxetine, fluoxetine, sertraline, citalopram and fluvoxamine. Coadministration of these agents with CYP2D6-metabolized drugs should be closely monitored or avoided. The coadministration results in a marked increase in plasma levels of the drug with the lower affinity for CYP2D6. These interactions depend on the affinity for CYP2D6 but also on the plasma level of the coadministered drugs. A drug with high CYP2D6 affinity but low plasma concentration will probably induce none or a minor drug interaction without clinical implications.

This problem of drug interaction is more intricate due to the fact that many drugs are biotransformed through several metabolic pathways using different isoenzymes (mainly CYP2C19, but also CYP3A4) and some of them are also subject to genetic polymorphism.

Our experience with fluoxetine, fluvoxamine and citalopram antidepressant interactions

In practice, our experience is in agreement with the literature (Baumann 1998; Solai et al. 2001) in that it showed that the most important difference between various SSRIs is represented by their differing potential to cause drug-drug interactions. As an example we shall discuss below the interaction between SSRIs and tricyclic antidepressants that are used by some physicians as one of the therapeutic strategies for treatment-resistant depression.

• Interactions are more frequent with fluoxetine and fluvoxamine:

Fluoxetine

Fluoxetine and its active metabolite, (S)-norfluoxetine, are mainly N-demethylated by CYP2D6. CYP3A4 also seems to play a role in their biotransformation. These molecules are potent inhibitors of CYP2D6 (Brosen and Skjelbo 1991). As CYP2D6 metabolism may be saturated when this antidepressant is prescribed, in the case of comedication drug interactions may appear, leading to drug overdose and side effects.

In our study on 29 phenotyped depressed inpatients receiving clomipramine, 10 days after the addition of 20 mg per day of fluoxetine, six patients switched from the extensive metaboliser 2D6 phenotype to a poor metaboliser phenotype (for materials and methods, see Vandell et al. 1995). This means that the 2D6 drug metabolic pathway was saturated, inducing the risk of overdose with all drugs using this biotransformation system. Concerning clomipramine, comedication with fluoxetine leads to a significant increase ($p < 0.02$) of the demethylclomipramine plasma levels.

In another study (for materials and methods, see Vandell et al. 1992) we found a quantitative difference between the fluoxetine-tricyclic antidepressant interaction. The increase of plasma levels appeared especially high with clomipramine and imipramine and lower with amitriptyline. Surprisingly, the pharmacokinetic change did not induce side effects in the patients. However, the total tricyclic antidepressant plasma levels were increased above the level around 500 ng/ml, which is considered toxic (clomipramine 965 ng/ml and imipramine 785 ng/ml). It should be noted that the patients in this study were not elderly.

These fluoxetine interactions by enzymatic

inhibition may be counteracted by other types of pharmacokinetic interaction such as enzymatic induction. We observed this in a patient treated with antidepressants, firstly amitriptyline, then amitriptyline together with fluoxetine, who then required antituberculosis treatment (rifampicin). When fluoxetine was added to amitriptyline (AMT), we observed, as expected, an increase in the plasma level of AMT and its metabolite, despite a decrease of its dosage. When antituberculosis treatment was added to the two antidepressants, a decrease of the tricyclic drug plasma levels was observed. It appeared that the fluoxetine interaction disappeared due to a competitive interaction (Bertschy et al. 1994).

All the drug interactions induced by comedication with fluoxetine may remain present for a long time after it is discontinued, due to its long half-life. In patients treated for several weeks or months with fluoxetine we observed that the drug was still detectable a month after its discontinuation (for more information, see Vandell et al. 1994).

Fluvoxamine

Fluvoxamine and fluoxetine differ in their interaction with the metabolism of some basic psychotropic drugs. Fluvoxamine seems not to be a major inhibitor of CYP2D6 but a potent inhibitor of other CYP (1A2 and 2C9) (Christensen et al. 2002). However, both CYP2D6 and CYP1A2 pathways seem to become saturated as fluvoxamine dosage increases (Spigset et al. 2001). Moreover, fluvoxamine possesses several metabolites that use the same biotransformation pathways. In our study on 29 inpatients receiving fluvoxamine treatment (150 mg/d) (for materials and methods, see Vandell et al. 1995), amitriptyline and clomipramine plasma levels increased and desmethylclomipramine plasma levels decreased. This was due to a blockade of clomipramine demethylation. The CYP2D6 metabolic capacity switched towards that of a poor metaboliser in two patients.

• Interactions are less frequent with:

Citalopram

Biotransformation of citalopram appears to be dependent on CYP2C19, CYP2D6 and CYP3A4 (Sindrup et al. 1993; Olesen and Linnet 1999). However, it is not a potent inhibitor of these isoenzymes and only a few drug interactions may be expected in the case of comedication. However, we detected some with clomipramine in a patient heterozygous for the CYP2D6 genotype and with a poor metaboliser status (for materials and methods, see Haffen et al. 1999a). After addition of citalopram, a desmethylclomipramine plasma level increase was observed, with a decrease of its hydroxylated metabolite.

We have no personal data on the most recently marketed antidepressants, but we did not observe marked pharmacokinetic interactions

with our therapeutic drug monitoring of the TCAs. Regarding mirtazapine, it is mainly mediated by the CYP2D6 and CYP3A4 isoenzymes but has few inhibitory effects on these enzymes (Timmer et al. 2000).

There is evidence that individual SSRIs display a distinct profile of cytochrome P450 inhibition. Data in the literature also show that fluoxetine, fluvoxamine and paroxetine are more likely to be involved in significant drug-drug interactions than are citalopram and sertraline (Baumann 1998; Solai et al. 2001). Regarding the problem of age, the pharmacokinetics of sertraline seem to be the same in both elderly and younger patients, whereas elderly patients may develop higher plasma levels of fluoxetine or paroxetine than younger patients when given the same dose (Preskorn 1993). Thus, citalopram and sertraline have several pharmacological advantages over other SSRIs for the treatment of elderly depressed patients. However, the increase of the prescription rates of SSRIs in elderly patients has had a financial impact with a cost increase of 61% between 1993 to 1997 (Mamdami et al. 2000).

Conclusion

As older people are prone to drug side effects, tricyclic antidepressants have to be used carefully due to their numerous adverse effects. Second generation antidepressants offer advantages as they have milder adverse effects, a better cardiac tolerability and a lower toxicity in overdose. However, as they are often given in co-medication, some precautions must be taken with respect to drug interactions. For this reason, and due to the different metabolic capacity of patients, drug combinations with SSRIs should be assessed on an individual basis (Bonin and Vandel 1995; Hemeryck and Belpaire 2002). In some cases, therapeutic drug monitoring or assessment of the genetically determined variability in drug concentration in individual patients may contribute to improving the therapeutic effect and to reducing the risk of dropouts due to tolerability problems (Rasmussen and Brosen 2000). These useful precautions, linked to age-related changes in pharmacokinetics, are probably one solution to improve treatment. However, they are not the only nor a miraculous solution, since another problem must be taken into account: in the elderly there are ultra structural changes of the brain neurones inducing pharmacodynamic changes and an increased cerebral vulnerability. A change in the number of receptors and in binding affinity has been described (Montamat et al. 1989). The dopaminergic limbic system is also sensitive to ageing, and this may be associated with cognitive impairment (Barili et al. 1998). Cholinergic and purinergic peripheral neurotransmissions are age-related. These changes may contribute to the poor tolerance of anticholinergic drug adverse effects in the elderly, for example (Yoshida et al. 2001).

Thus, depending on the antidepressant class choice and the physiological state of the patient, clinical and biological monitoring will be necessary. So, as Baldwin said, "it is – perhaps – unnecessary to pit one class of antidepressants against another: there is room for both" (Baldwin 1999).

References

- Alexanderson B, Evans DA, Sjöqvist F (1969) Steady state plasma levels of nortriptyline in twins: influence of genetic factors and drug therapy. *Br Med J* 4: 764-768.
- Baldwin RC (1999) Antidepressants for old people. GPs should become familiar with one or two antidepressants from each class. *BMJ (Letters)* 319: 849.
- Baldwin RC (2000) Poor prognosis of depression in elderly people: causes and actions. *Ann Med* 32: 252-256.
- Barili P, De Carolis G, Zaccheo D, Amenta F (1998) Sensitivity to ageing of the limbic dopaminergic system: a review. *Mech Ageing Dev* 106: 57-92.
- Baumann P (1998) Care of depression in the elderly: comparative pharmacokinetics of SSRIs. *Int Clin Psychopharmacol* 13 (Suppl 5): S35-S43.
- Bertilsson L (1995) Geographical/interracial differences in polymorphic drug oxidation. Current state of knowledge of cytochromes P450 (CYP) 2D6 and 2C19. *Clin Pharmacokinet* 29: 192-209.
- Bertilsson L, Dahl ML, Tybring G (1997) Pharmacogenetics of antidepressants: clinical aspects. *Acta Psychiatr Scand* 391(Suppl): 14-21.
- Bertschy G, Vandel S, Perault MC (1994) A case of metabolic interaction: amitriptyline, fluoxetine, antitubercular agents. *Therapie* 49: 509-512.
- Bonin B, Vandel S (1995) Drug interaction and new antidepressive agents. *Thérapie* 50: 229-236.
- Brosen K, Gram L (1989) Clinical significance of the sparteine/debrisoquine oxidation polymorphism. *Eur J Clin Pharmacol* 36: 537-547.
- Brosen K, Skjelbo E (1991) Fluoxetine and norfluoxetine are potent inhibitors of P450IID6—the source of the sparteine/debrisoquine oxidation polymorphism. *Br J Clin Pharmacol* 32: 136-137.
- Butler RN, Lewis MI (1995) Late-life depression: when and how to intervene. *Geriatrics* 50: 44-46.
- Cadieux RJ (1999) Antidepressant drug interactions in the elderly. Understanding the P-450 system is half the battle in reducing risks. *Postgraduate medicine* 106: 231-249.
- Christensen M, Tybring G, Mihara K, Yasui-Furokori N, Carrillo JA, Ramos SI, Anderson K, Dahl ML, Bertilsson L (2002) Low daily 10-mg and 20-mg doses of fluvoxamine inhibit the metabolism of both caffeine (cytochrome P4501A2) and omeprazole (cytochrome P4502C19). *Clin Pharmacol Ther* 71: 141-152.
- Cole MG (2000) Recurrence of geriatric depression. *Am J Psychiatry* 157: 1183-1184.
- Coutts RT, Urchuk LJ (1999) Polymorphic cytochromes P450 and drugs used in psychiatry. *Cell Mol Neurobiol* 19: 325-354.
- Dahl ML, Sjöqvist F (2000) Pharmacogenetic methods as a complement to therapeutic monitoring of antidepressants and neuroleptics. *Ther Drug Monit* 22:114-117.

de Mendonça Lima CA, Eap CB, Baumann P (2000) La psychopharmacothérapie dans le domaine de la psychogériatrie: actualités, problèmes, perspectives. *Rev Med Suisse Romande* 120: 131-136.

Gareri P, Falconi U, De Fazio P, De Sarro G (2000) Conventional and new antidepressant drugs in the elderly. *Prog Neurobiol* 61: 353-396.

Gurvich T, Cunningham JA (2000) Appropriate use of psychotropic drugs in nursing homes. *Am Fam Physician* 61: 1437-1446.

Gurwitz JH, Field TS, Avorn J, McCormick D, Jain S, Eckler M, Benser M, Edmondson AC, Bates DW (2000) Incidence and preventability of adverse drug events in nursing homes. *Am J Med* 109: 87-94.

Haffen E, Vandel P, Broly F, Vandel S, Sechter D, Bizouard P, Bechtel P (1999a) Citalopram: an interaction study with clomipramine in a patient heterozygous for CYP2D6 genotype. *Pharmacopsychiatry* 32: 232-234.

Haffen E, Vandel P, Paintaud G, Broly F, Vandel S, Bonin B, Bizouard P, Sechter D, Bechtel P (1999b) Influence of CYP2D6*2 and CYP2D6*4 alleles on phenotype in polymedicated depressed inpatients: therapeutic consequences? *Eur J Clin Pharmacol* 55: 877-879.

Hammer W, Sjöqvist F (1967) Plasma levels of monomethylated tricyclic antidepressants during treatment with trimipramine-like compounds. *Life Sci* 6: 1895-1903.

Hemeryck A, Belpaire FM (2002) Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab* 3: 13-37.

Herrmann N (2000) Use of SSRIs in the elderly: obvious benefits but unappreciated risks. *Can J Clin Pharmacol* 7: 91-95.

Johansson I, Lundqvist E, Bertilsson L, Dahl ML, Sjöqvist F, Ingelman-Sundberg M (1993) Inherited amplification of an active gene in the cytochrome P450 CYP2D locus as a cause of ultra-rapid metabolism of debrisoquine. *Proc Natl Acad Sci USA* 90: 11825-11829.

Kalow W, Bertilsson L (1994) Interethnic factors affecting drug response. *Adv Drug Res* 25: 1-53.

Katona C (2000) Managing depression and anxiety in the elderly patient. *Eur Neuropsychopharmacol* 10(Suppl 4): S427-S432.

Kirchheiner J, Brosen K, Dahl ML, Gram LF, Kasper S, Roots J, Sjöqvist F, Spina E, Brockmüller J (2001) CYP2D6 and CYP2C19 genotype-based dose recommendation for antidepressants: a first step towards subpopulation-specific dosages. *Acta Psychiatr Scand* 104: 173-192.

Leonard BE (1992) Pharmacological differences of serotonin reuptake inhibitors and possible clinical relevance. *Drugs* 43: 3-9.

Mahgoub A, Idle JR, Dring LG, Lancaster R, Smith RL (1977) Polymorphic hydroxylation of debrisoquine in man. *Lancet* 2: 584-586.

Maletta G, Mattox KM, Dysken M (2000) Update 2000. Guidelines for prescribing psychoactive drugs. *Geriatrics* 55: 65-72.

Mamdami MM, Parikh SV, Austin PC, Upshur RE (2000) Use of antidepressants among elderly subjects: trends and contributing factors. *Am J Psychiatry* 157: 360-367.

Menting JE, Honig A, Verhey FR, Hartmans M, Rozendaal N, de Vet HC, van Praag HM (1996) Selective serotonin reuptake inhibitors (SSRIs) in the treatment of elderly depressed patients: a qualitative analysis of the literature on their efficacy and side effects. *Int Clin Psychopharmacol* 11: 165-175.

Meyer UA, Zanger UM (1997) Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol* 37: 269-296.

Montamat SC, Cusack BJ, Yestal RE (1989) Management of drug

therapy in the elderly. *New Engl Med* 321: 303-309.

Olesen O, Linnet K (1999) Studies on the stereoselective metabolism of citalopram by human liver microsomes and cDNA-expressed cytochrome P450 enzymes. *Pharmacology* 59: 298-309.

Preskorn SH (1993) Recent pharmacologic advances in antidepressant therapy for the elderly. *Am J Med* 94: 25-125.

Raimundo S, Fischer J, Eichelbaum M, Griese E, Schwab M, Zanger U (2000) Elucidation of the genetic basis of the common "intermediate metabolizer" phenotype for drug oxidation by CYP2D6. *Pharmacogenetics* 10: 577-581.

Rasmussen BB, Brosen K (2000) Is therapeutic drug monitoring a case for optimizing clinical outcome and avoiding interactions of the selective serotonin reuptake inhibitors? *Ther Drug Monit* 22: 143-154.

Rojas-Fernandez C, Thomas VS, Carver D, Tonks R (1999) Suboptimal use of antidepressants in the elderly: a population-based study in Nova Scotia. *Clin Ther* 21: 1937-1950.

Sindrup SH, Brosen K, Hansen MG, Aaes Jorgensen T, Overo KF, Gram L (1993) Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. *Ther Drug Monit* 15: 11-17.

Solai LK, Mulsant BH, Pollock BG (2001) Selective serotonin reuptake inhibitors for late-life depression: a comparative review. *Drugs Aging* 18: 355-368.

Spigset O, Axelsson S, Norstrom A, Hagg S, Dahlqvist R (2001) The major fluvoxamine metabolite in urine is formed by CYP2D6. *Eur J Clin Pharmacol* 57: 653-658.

Steffens DC, Skoog I, Norton MC, Hart AD, Tschanz JT, Plassman BL, Wyse BW, Welsh-Bohmer KA, Breitner JC (2000) Prevalence of depression and its treatment in an elderly population: the Cache County study. *Arch Gen Psychiatry* 57: 601-607.

Strik JJ, Honig A, Lousberg R, Cheriex EC, Van Praag HM (1998) Cardiac side-effects of two selective serotonin reuptake inhibitors in middle-aged and elderly depressed patients. *Int Clin Psychopharmacol* 13: 263-267.

Timmer CJ, Sitsen JM, Delbressine LP (2000) Clinical pharmacokinetics of mirtazapine. *Clin Pharmacokinet* 38: 461-474.

Turnheim K (2000) Adverse effects of psychotropic drugs in the elderly. *Wien Klin Wochenschr* 112: 394-401.

Unutzer J, Simon G, Belin TR, Datt M, Katon W, Patrick D (2000) Care for depression in HMO patients aged 60 and older. *J Am Geriatr Soc* 48: 871-878.

Vandel S, Bertschy G, Bonin B, Nezelof S, Francois TH, Vandel B, Sechter D, Bizouard P (1992) Tricyclic antidepressant plasma levels after fluoxetine addition. *Neuropsychobiology* 25(4): 202-207.

Vandel S, Bertschy G, Bouquet S, Bonin B, Vittouris N (1994) Fluoxetine and norfluoxetine plasma levels after treatment discontinuation in man. *Thérapie* 49: 141-142.

Vandel S, Bertschy G, Baumann P, Bouquet S, Bonin B, Francois T, Sechter D, Bizouard P (1995) Fluvoxamine and fluoxetine: interaction studies with amitriptyline, clomipramine and neuroleptics in phenotyped patients. *Pharmacol Res* 31: 347-353.

Vandel P, Haffen E, Vandel S, Bonin B, Nezelof S, Sechter D, Broly F, Bizouard P, Dalery J (1999) Drug extrapyramidal side effects. CYP2D6 genotypes and phenotypes. *Eur J Clin Pharmacol* 55(9): 659-665.

Wilson KC, Copeland JR, Taylor S, Donoghue J, McCracken CF (1999) Natural history of pharmacotherapy of older depressed community residents. The MCR-ALPHA study. *Br J Psychiatry* 175: 439-443.

Woo MH, Smythe MA (1997) Association of SIADH with selective serotonin reuptake inhibitors. *Ann Pharmacother* 31: 108-110.

Yamada H, Dahl ML, Lannfelt L, Viitanen M, Winblad B, Sjöqvist F (1998) CYP2D6 and CYP2C19 genotypes in an elderly Swedish population. *Eur J Clin Pharmacol* 54: 479-481.

Yoshida M, Homma Y, Inadome A, Yono M, Seshita H, Miyamoto Y, Murakami S, Kawabe K, Ueda S (2001) Age-related changes in cholinergic and purinergic neurotransmission in human isolated bladder smooth muscles. *Exp Gerontol* 36: 99-109.

Reconsidering the Classification of Schizophrenia and Manic Depressive Illness – A Critical Analysis and New Conceptual Model

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Summary

The idea of 'disease entity' in psychiatry and the nosologic map of insanity with the distinction between dementia praecox (schizophrenia since Bleuler 1911) and manic depressive insanity, originally developed by Emil Kraepelin (1896), is an important landmark in the history of psychiatry (Jablensky 1995). This classification, however, has been vigorously debated throughout the years, and new evidence emerging from epidemiological, clinical, genetic and biological research demonstrates that the two nosological categories have distinct features as well as share many similarities in their risk factors, genetic predisposition, brain pathology, neurophysiology, clinical phenomenology and response to treatment, thus raising questions about the validity of the categorical classification of psychoses.

In this paper we examine some of the similarities and differences between schizophrenia and bipolar illness emerging from recent biological and clinical research and attempt to clarify major inherent logical contradictions in the application of the 'disease' model of psychiatric diagnosis to the categorical classification of schizophrenia and bipolar illness. Then we examine how similar predicaments have been resolved in other natural classification systems, namely the biological classification of species and the periodic table of the elements. Finally we propose a hypothetical conceptual approach to the classification of psychoses that has been greatly informed by the organizing principle underlying the periodic table of the elements, and is distinct from the 'disease' model of psychiatric classification.

Keywords: schizophrenia, bipolar illness, psychosis, classification.

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Introduction

The modern classification of psychoses has been a topic of vigorous debate ever since its inception with the formulation of the disease concepts of dementia praecox and manic-depressive insanity by Emil Kraepelin in 1896 and their subsequent codification into the nosologic entities of schizophrenia and bipolar illness (Jablensky 1999a; Torrey and Knable 1999; Murray et al. 1985). The validity of this classification has been iteratively re-examined in the light of every new line of evidence produced by the continuous development of new research tools and methods of investigation. In this context no question has been more actively debated than whether schizophrenia and manic depressive illness are distinct or related, and potentially overlapping illnesses. On one hand there is the view originated by Kraepelin that regarded the two entities as discontinuous disorders that were qualitatively distinct (Kraepelin 1896) though with partially overlapping phenomenology and natural histories, while on the other hand schizophrenia and manic depressive illness were regarded as qualitatively similar disorders that were on a pathological continuum of mental illness previously referred to as the endogenous psychoses (Crow 1990; Curtis et al. 2000). The tremendous recent advances in molecular neuroscience, structural and functional neuroimaging, and genetics have contributed evidence suggesting that schizophrenia and bipolar illness share many similarities as well as have distinct features in their risk factors and genetic predisposition, brain pathology and neurophysiology, clinical phenomenology and response to treatment (Wildenauer et al. 1999; Buka and Fan 1999; Jones and Tarrant 1999; Goldberg 1999; Pearlson 1999; Post 1999; Curtis et al. 2000). It appears, however, that the same evidence from the comparative epidemiological, clinical and biological studies could be interpreted in at least two different ways that lead to contradicting conclusions regarding the validity of the current classification paradigm, thus

rendering the categorical classification of psychoses neither universally validated, nor unequivocally rejected. Hence, the continuing debate on this topic.

Contributing to the debate that has engaged some of the most brilliant thinkers in the field of psychiatry and consumed “forests of paper and gallons of ink” (Torrey and Knable 1999), is a formidable task. Nonetheless, we are motivated to contribute to this debate to make the point that the century-old uncertainty about the validity of the categorical classification of psychotic ‘diseases’ is an indication that new classification paradigms should be more actively sought, conceptualised and tested in practice.

In our attempt to provide a useful point of view in the debate regarding the classification of psychoses we will begin by first summarizing the recurring themes emerging from recent epidemiological, clinical and biological studies of schizophrenia and bipolar illness. Then we will discuss how the evident similarities and differences between the two conditions are traditionally interpreted in the light of the question “Are schizophrenia and bipolar illness two diseases or one?” and will seek to determine whether in fact this question has a legitimate answer. In this context we will attempt to reason whether the notion of a ‘disease’, which is central to the current classification paradigm of psychoses, provides an adequate framework for rationalization and true understanding of the similarities and differences among different diagnostic categories. In the discussion section we will compare the classification of psychoses to some other well-validated classification systems in biology and chemistry and will examine how concepts underlying the biological classification of species and the periodic table of the elements could inform our thinking about the classification of psychoses. And finally, we would like to suggest a possible new direction for the future evolution of the classification of mental illnesses.

Validating criteria for psychiatric diagnosis

The categorization of major psychoses into dementia praecox and manic-depressive insanity proposed by Kraepelin in 1896 was the result of rigorous observation and documentation of clinical presentation, course and outcome of the hypothetical ‘disease entities’. The current approach to the diagnoses of schizophrenia and bipolar illness, as reflected in DSM-IV and ICD-10, is also based on phenomenological/behavioural description of psychopathology. In concordance with this organizing principal of the categorical classification of major psychoses, contemporary systematic investigation of the internal coherence of the nosological entities of schizophrenia and bipolar illness is focusing on

the clinical description (or the content validity of the classification), delimitation from other disorders (or the discriminant validity), and evidence from laboratory, family and follow-up studies (to test the criterion-related validity; Robins and Guze 1970; Cloninger 1989). It is important to note that in this validation process, the converging evidence from neuroimaging, genetic and other laboratory studies is regarded as secondary evidence supporting a classification that is primarily based on clinical symptomatology, rather than being an independent organizing principle of classification.

Content and discriminant validity (clinical description, diagnostic stability over time, delimitation from other disorders)

The clinical phenomenology of both schizophrenia and bipolar illness substantially overlap, including positive psychotic symptoms, negative, cognitive and mood symptoms. At the same time there are also many differences. In schizophrenia the psychotic symptoms are generally mood-incongruent; the mood symptoms are moderately frequent, less severe, and are not a dominant symptom cluster; the negative symptoms of diminished internal drive and volition affect most patients (whereas they are not found in bipolar disorder), and cognitive deficits in working memory, attention and executive functions are a cardinal feature. The cardinal feature of bipolar illness is mood symptoms, with the negative and cognitive symptoms being much less frequent and severe. The psychotic features of bipolar illness are generally mood-congruent. Consequently, by using operational diagnostic criteria most patients with psychotic illness can be classified reliably, but due to the substantial overlap in the cross-sectional symptomatology of schizophrenia and bipolar illness some individuals cannot be unequivocally classified as members of either category. For example the multicentre trial of the ICD-10 criteria resulted in a kappa of 0.84 for all schizophrenic disorders and a kappa of 0.83 for the diagnosis of bipolar disorder (Sartorius et al. 1995). The longitudinal course of schizophrenia and bipolar illness is also characterized by significant overlap and periodic cross-over. Although Kraepelin initially distinguished the two illnesses by the progressive nature and consequent clinical deterioration associated with schizophrenia but not bipolar disorder, some proportion of bipolar patients also exhibit deterioration, albeit less severely. In the International Pilot Study of Schizophrenia 17% of subjects who were initially diagnosed as schizophrenic developed at least one affective episode in the subsequent course of their illness. Conversely, 8% of patients originally diagnosed as manic later developed persistent schizophrenic symptomatology (Sheldrick et al. 1977). Similar results were reported in the subsequent WHO 10-country study (Jablensky et al. 1992; Wiersma et al. 1998).

Unique evidence for the diagnostic stability over time and the internal consistency and discrimination between dementia praecox and manic-depressive insanity is provided by the study of Jablensky and colleagues (Jablensky et al. 1993) who carried out a meta-analysis on 53 cases of Dementia Praecox (DP) and 134 cases of manic-depressive insanity (MDI) originally diagnosed by Kraepelin in Munich in 1908. A CATEGO reclassification of the patients found >80% concordance between Kraepelin’s diagnoses and ICD-9. Cluster analysis of the original case material, coded in terms of Present State Examination syndromes, “reproduced closely Kraepelin’s dichotomous classification of the psychoses but suggested that DP was a narrower concept than schizophrenia today, while MDI was a composite group including both ‘typical’ manic-depressive illnesses and schizoaffective disorders” (Jablensky et al. 1993). A Grade of Membership analysis of the same clinical material did not fully support the dichotomy of dementia praecox and manic-depressive insanity. The catatonic syndrome tended to occupy an intermediate position between the two major psychoses (Jablensky and Woodbury 1995).

• Comparative epidemiology, risk factors and premorbid antecedents

Epidemiological comparisons reveal that schizophrenia and bipolar illness have some common risk factors and premorbid antecedents as well as distinct epidemiological features on the basis of which the two disorders could be differentiated (Torrey 1999). Schizophrenia occurs in all populations with prevalence in the range of 1.4 to 4.6 per 1000 and incidence rates in the range of 0.16-0.42 per 1000 population (Jablensky 2000). Most prevalence studies of schizophrenia and bipolar illness have reported that overall schizophrenia is 1.5-2 times more prevalent (Torrey 1999), however, there are marked differences in the comparative 6-month prevalence per 1000 of schizophrenia and mania among different geographic areas (Burnam et al. 1987). Both schizophrenia and bipolar disorder occur equally in males and females, though the age of onset for schizophrenia is earlier in males (Torrey 1999; Jablensky 1997). The risk factors shared by both disorders include excess of winter-spring births, abnormal dermatoglyphics, and an excess of prenatal and perinatal complications (Torrey 1999; Buka and Fan 1999). By contrast, an excess of urban births and minor physical abnormalities are present in schizophrenia, but not in bipolar illness (Torrey 1999). Perhaps some of the most robust epidemiological differences distinguishing the two disorders are the more frequent description of geographic isolates for bipolar disorder (Egeland 1988; Morissette et al. 1999; Freimer et al. 1996; Pekkarinen et al. 1995) and the higher prevalence of bipolar illness in the higher socio-economic groups (Goodwin and Jamison 1990).

Developmental abnormalities that have been identified in individuals who later develop schizophrenia and bipolar illness include delayed motor and language skills, poorer educational achievement, neurological signs such as poorer balance and coordination, clumsiness, excess tics and twitches (Jones et al. 1994; van Os et al. 1997; Done et al. 1994; Crow et al. 1995; Crow 1998). These findings appear to be less pronounced for individuals destined to develop bipolar illness (van Os et al. 1997; Jones and Tarrant 1999). Deficits in sociability and personality have been identified specifically in the premorbid stages of schizophrenia, but not affective illness (Jones et al. 1994; van Os et al. 1997).

Criterion-related validity (biological features)

Magnetic resonance imaging (MRI) studies reveal that both schizophrenia and bipolar illness may have increased ventricular volume (Johnstone et al. 1976; Shenton et al. 2001; Pearlson and Veroff 1981; Botteron et al. 1995). In addition patients with schizophrenia have preferential involvement of medial temporal lobe structures, which include the amygdala, hippocampus and parahippocampal gyrus, and neocortical temporal lobe regions (superior temporal gyrus), along with frontal lobe abnormalities, particularly prefrontal grey matter and orbitofrontal regions (Shenton et al. 2001). In contrast, in bipolar illness there have been consistent reports of deep subcortical white matter signal hyperintensities (McDonald et al. 1991; Botteron et al. 1995; Aylward et al. 1994).

There is a growing body of evidence of a fundamental neurointegrative dysfunction in schizophrenia, which is reflected in deficits in sustained attention, working memory, verbal fluency and executive functions (Kremen et al. 2001). Recent studies directly comparing the cognitive abnormalities in schizophrenia and bipolar illness provide support for the view that patients with bipolar disorder suffer less severe cognitive impairment than do patients with schizophrenia (Goldberg 1999; Seidman et al. 2002), though patients with bipolar illness have also demonstrated abnormalities on measures of sustained attention and Span of Apprehension (Addington and Addington 1998), on measures of declarative verbal memory, abstraction, perceptual-motor speed and vigilance (Seidman et al. 2002), and on visuospatial tasks (El Badri et al. 2001), relative to healthy individuals. It is still unclear whether the similarities of higher order neurocognitive dysfunction in schizophrenia in comparison to bipolar illness represent differences in degree or type of abnormalities (Goldberg 1999; Hawkins et al. 1997; Seidman et al. 2002).

Evidence provided by recent family studies indicates that the two conditions are more closely related genetically than is generally

believed. Increased morbid risk for schizophrenia has been reported in families of patients with bipolar illness (Valles et al. 2000). The same study also found that the presence of more than one patient with bipolar disorder in a family increased the risk for schizophrenia nearly fourfold. Kendler and Hayes (1983) reported that when compared to schizophrenics with no relatives with affective disorder, the schizophrenic patients with a relative with bipolar illness were more depressed during their prodromal phase, were more elated and catatonic when actively psychotic, had fewer residual symptoms when remitted, and were much more likely to have a manic syndrome develop during the follow-up period. In a different study Kendler and Tsuang (1988) reported findings consistent with the hypothesis that the liability to affective illness may influence outcome in schizophrenia. Taken together the evidence derived from family studies suggests that the genetic transmission of psychosis is not diagnosis-specific and may be an indication of shared vulnerability between affective and non-affective psychoses.

A similar conclusion is also supported by recent genetic studies reporting unique as well as shared DNA susceptibility loci. Unique schizophrenia susceptibility loci that are believed to be independent from the genetic loci associated with bipolar illness are identified on chromosome 6p22-24 (Wang et al. 1995; Moises et al. 1995; Schwab et al. 1995; Straub et al. 1996); 8p21-24 (Kendler et al. 1996; Blouin et al. 1998; Gurling et al. 2001); 6q21 (Cao et al. 1997; Martinez et al. 1999; Levinson et al. 2000); and 1q (Brzustowicz et al. 2000; Gurling et al. 2001). Chromosomal associations unique for bipolar illness are documented on chromosome 21q21 (Straub et al. 1994; Detera-Wadleigh et al. 1996; Kelsoe et al. 2001; Smyth et al. 1997; Kwok et al. 1999); 18q22 (Stine et al. 1995; McMahon et al. 1997; McInnes et al. 1996; Coon et al. 1996); 4pter (Blackwood et al. 1996; Ewald et al. 1998b); and 12q24 (Morissette et al. 1999; Ewald et al. 1998a). In addition several other loci appear to be common for both schizophrenia and bipolar disease kindreds on chromosome 18p11 (Berrettini 2000); 13q32 (Blouin et al. 1998; Detera-Wadleigh et al. 1999; Brzustowicz et al. 1999); 22q11 (Detera-Wadleigh et al. 1999; Kelsoe et al. 2001); and 10p14 (Faraone et al. 1998; Schwab et al. 1998; Foroud et al. 2000).

• Comparative pharmacology

The pharmacological treatment of an acute psychotic episode in schizophrenia and the treatment of an acute manic episode overlap considerably in terms of use of both typical and atypical antipsychotic medications (Post 1999). Antidepressant drugs and high-potency benzodiazepines are good adjunctive agents for both bipolar illness and for depressive and anxiety symptoms associated with schizophrenia (Post

1999). The treatments of bipolar illness and schizophrenia begin to differentiate in the use of mood stabilizers, such as lithium, carbamazepine and valproate, which show a lesser degree of efficacy in schizophrenia in comparison to affective illness (Post 1999), although the anti-convulsants are used extensively as adjunctive agents to antipsychotic drugs. Also, the calcium channel blocker verapamil has been shown to be effective in mania, but it may exacerbate symptoms of schizophrenia (Brunet et al. 1990; Pazzaglia et al. 1998, 1993; Pickar et al. 1987). It is noteworthy, however, that individual response to particular therapeutic agents from the different pharmacological classes is highly unpredictable even for patients with the same clinical diagnosis. And sometimes patients with different clinical diagnoses demonstrate remarkable responsiveness to the same medication; clozapine in particular has been shown to be effective in treating some patients with mania as well as patients with schizophrenia (Frye et al. 1998). At present there are no established biological markers predicting response to specific medications and identifying the most appropriate treatment for a person diagnosed with either schizophrenia or bipolar illness still remains a matter of trial and error. It appears that the clinical diagnosis serves as a rough guide for choosing the type of first-line or adjunctive treatment (i.e. an antipsychotic versus a mood stabilizer versus an antidepressant) rather than the specific pharmacological agent from within a given class.

Alternative classification models

The lack of a precise diagnostic boundary between schizophrenia and bipolar illness has long been recognized. Kraepelin himself, in one of his latest publications, wrote: "Perhaps it is also possible to tackle the difficulties, which prevent us from distinguishing reliably between manic-depressive insanity and dementia praecox. No experienced psychiatrist will deny that there is an alarmingly large number of cases in which it seems impossible, in spite of the most careful observations, to make a firm diagnosis. Nevertheless, the fact that we cannot distinguish satisfactorily between these two illnesses raises the question of whether our diagnostic formulation may be incorrect" (Kraepelin 1920). Attempts to overcome the limitations of the categorical classification of psychoses have led to the formulation of an alternative concept that the phenomenology of psychosis is a 'continuum' extending from unipolar, through bipolar affective illness and schizoaffective psychosis, to typical schizophrenia (Crow 1990; Curtis et al. 2000). It appears that the idea of continuous psychopathological states of mind, as described in Crow (1990) and Curtis (Curtis et al. 2000) reflects the content-related characteristics of the patients' mental experiences, which are, arguably, very

difficult to operationalise and force into a discrete categorical classification scheme. This view, however, does not address the question of how the 'continuum of psychosis' relates to other psychopathological states and how the model of psychosis fits in the general picture of psychiatric classification. And while this model may better represent the clinical reality of individual cases and may be more intuitively appealing to clinicians, it is yet to be demonstrated that the continuous model could potentially enhance our understanding of the genetic basis and pathophysiology of psychosis beyond the dichotomous model.

An alternative, dimensional strategy attempts to transcend the content-related aspects of psychopathological presentation and identify the fundamental or generic properties (or axes) underlying a particular phenomenon (phenomena) within or across traditional diagnostic groups and content types (van Os et al. 1996; Appelbaum et al. 1999; Karakula and Grzywa 1999; Oulis et al. 2000; Banaschewski et al. 2000). To date, however, experts in the field have failed to agree on the number of relevant dimensions and no single dimensional model of psychosis appears to be sufficiently validated. A more general problem associated with the core statistical apparatus of the dimensional approach is that the methodology does not permit quantitative comparisons among individuals with respect to the pertinent dimensions identified in a particular model. In factor analysis, for example, the focus is on identifying clusters of variables from pairwise correlations of covariances. The correlations do not retain information on individuals thereby precluding the decomposition of the properties of individuals. The implications of this statistical limitation for the potential usefulness of the pure dimensional approach to psychosis and psychiatric classification in general are manifold. The dimensions underlying a particular phenomenon or state of mind, by not carrying information about the subjects who possess them, acquire an abstract existence of their own that renders clinical interpretation very difficult. Also, at present genetic and other biological studies depend on comparisons between a group of individuals who possess a trait or phenotype of interest, and a group of individuals who do not. While the pure dimensional approach is suited for identifying alternative phenotypes for genetic or other biological studies, it does not enable investigators to distinguish between the cases that have or do not have the phenotype of interest.

Another strategy for approaching the issue of psychiatric classification has been the combination of the categorical and dimensional models by means of a new statistical procedure, Grade of Membership (GoM) analysis (Woodbury et al. 1978; Woodbury and Manton

1982). GoM is a multivariate classification procedure based on fuzzy-set mathematics that allows individuals to exhibit concurrent and partial membership to more than one diagnostic category. The GoM procedure simultaneously describes both the prototypical diagnostic classes (or 'pure types') that underlie multivariate sets of psychopathological or functional characteristics of individuals and quantifies the degrees to which an individual belongs to a pure type. The degrees of membership to a pure type could be used as a basis of either classifying or ascertaining individuals for biological studies. The GoM procedure has proven effective in dealing with complex sets of clinical data and has been used for generating classifications across a variety of traditional psychiatric and non-psychiatric conditions: schizophrenia (Jablensky and Woodbury 1995; Manton et al. 1994), mania (Cassidy et al. 2001), depression (Davidson et al. 1988; Davidson et al. 1989; Blazer et al. 1989), anxiety and somatization disorder (Piccinelli et al. 1999; Swartz et al. 1987), personality disorders (Nurnberg et al. 1999; Jordan et al. 1989), Alzheimer's disease (Corder and Woodbury 1993; Corder et al. 2000), and diabetes mellitus (Corder et al. 2001). It has been applied also in genetic studies of schizophrenia where the composite quantitative phenotypes generated by GoM have been used to detect linkage in a candidate region on chromosome 6, previously identified as a susceptibility locus for schizophrenia (Jablensky et al. 2002). The promising success of this work indicates that the Grade of Membership analysis may be a powerful statistical tool for increasing the phenotype resolution in genetic studies of psychiatric disorders that merits further attention.

Discussion

Classification is the process of grouping things together on the basis of the features they have in common. In medical sciences in general, and psychiatry in particular, the basic unit of classification is the 'disease'. The notion of a disease entity assumes that the 'disease' is represented by stable patterns of associations between clinical phenomenology, organ and cellular morphology, pathophysiology and aetiology. Diseases are thought to be discrete, mutually exclusive entities that could be clearly delineated from other diseases on the basis of some specific or pathognomonic characteristics. In case such specific signs are not available, diseases are recognized and classified on the basis of the internal consistency of their correlated clinical and biological features, course and outcome (Robins and Guze 1970; Cloninger 1989).

The collective evidence emerging from our analysis of the recent studies of schizophrenia and bipolar illness indicates that the two conditions have many similar as well as distinct

features in their genetic, epidemiological, neuroimaging, neurocognitive and clinical correlates and treatment (Wildenauer et al. 1999; Buka and Fan 1999; Jones and Tarrant 1999; Goldberg 1999; Pearlson 1999; Post 1999; Curtis et al. 2000). By using operational criteria the two nosological entities could be correctly identified in about 80% of cases, whereas approximately 20% of cases cannot be unequivocally classified as members of either diagnostic group. There is high, but not perfect temporal stability of the diagnostic categories of schizophrenia and bipolar illness (Jablensky et al. 1992, 1993; Sheldrick et al. 1977; Wiersma et al. 1998). Since both distinct and overlapping features have been identified on all levels of clinical, epidemiological and biological complexity, the notion of the 'disease' as a distinct entity of clinical and biological features does not appear capable of providing a definitive and valid decision between two possible opposing interpretations of the same evidence. If the differences between schizophrenia and bipolar illness are emphasized it could be concluded that despite the variable manifestations and overlap the two entities could indeed be regarded as two separate 'diseases' with considerable internal consistency and clinical and epidemiological validity. If the similarities between the dichotomous categories are favoured, it could be concluded that schizophrenia and bipolar illness represent the ends of a continuum of psychotic illnesses with overlapping psychopathology, biological features and aetiologic antecedents (Crow 1990; Curtis et al. 2000). However, at present we believe that there are no sufficiently developed alternative classification models to warrant change in the nosological categories, but at the same time feel that as new evidence emerges new organizing principles and classification approaches should be conceptualised and tested. One of the main purposes of diagnosis is to aid in the determination of prognosis and to guide treatment. Until evidence emerges that better assists clinicians in the clinical care of patients with schizophrenia and manic-depressive illness, there is not sufficient reason to alter these diagnostic entities.

We would like to address the discussion about the notion of a categorical versus continuous classification of psychoses by examining how a similar dilemma has been handled in some other classification systems, namely the biological classification of species and the periodic table of the elements. Then we will compare the classifications with respect to their organizing principles and will consider how some of the concepts underlying the biological classification of species and the periodic table could inform our thinking about the classification of psychiatric conditions. We chose to explore the classification of species and the periodic table of the elements because, despite some exceptions, they are well-validated natural classifications of all living

organisms, including humans, and their basic structural elements. The two classifications have proven significant practical and scientific merit and have provided both basis and stimulus for development of the biological and chemical sciences for over a century.

The core concept of the biological classification of living organisms is that of species. Species is a Latin word meaning 'kind' or 'appearance'. Biological species are defined as "groups of interbreeding natural populations that are reproductively isolated from other such groups" (Ernst Mayr, as cited in Campbel and Reece 2001). In other words species are groups of organisms that have the potential to interbreed with one another in nature and produce a fertile offspring, but who cannot produce such offspring when mating with members of other species. Hence species could be regarded as discrete, mutually exclusive entities that are sharply delimited from one another by a reproductive barrier. Sometimes it is very difficult to distinguish between different species on the basis of their physical characteristics. For example, the eastern meadowlark (*Sturnella magna*) and the western meadowlark (*Sturnella neglecta*) are very similar in appearance, yet they are classified as different species because they cannot interbreed (Campbel and Reece 2001). In contrast, other organisms, for example humans, that appear phenotypically diverse, belong to a single species defined by their capacity to interbreed. In essence, the biological classification of species is a categorical one. Continuous phenotypic characteristics that spread over several species are quite common, but insofar as they are different from the main functional characteristic defining the species, they do not challenge the basis of classification itself. In fact, the degree of similarity between closely related species is very useful for understanding the origin of the species and their evolutionary path, and constructing the supraordinate taxonomic categories of genus, family, order, class, phylum and kingdom. The categorical classification of species also allows for a great phenotypic diversity within the same group.

Similar interpretation of the categorical/continuous predicament emerged from our study of the periodic table of the elements as a classification system. The periodic classification of the elements depends upon the electron structure of atoms (Puddephatt and Monaghan 1986). Each new element in the table contains one more nuclear charge than the preceding element; this charge is neutralized by the addition of one electron placed into the lowest energy orbital available. The elements are then naturally classified into periods depending on which electron shell is being filled and into groups according to the maximum oxidation state of the elements. As in the biological classification of species, numerous similarities of physical

properties are evident in elements of different groups in the periodic table. For example, the elements of both groups I and II are metals with a typical metallic lustre and ability to conduct heat and electricity. Moreover, there is a well-pronounced continuous gradient of the metallic properties of the elements from left to right in the table. The elements of groups I and II are typical metals, the elements of groups VII and VIII are definite non-metals, and some elements in the middle groups are known as metalloids because their properties are intermediate between those expected for a metal and for a non-metal. For example, boron has a metallic lustre but is only a semiconductor of electricity (Puddephatt and Monaghan 1986).

As could be inferred from the biological classification of species and the periodic table of the elements, the presence of similar or continuous characteristics in members of different species or groups is not considered incompatible with the categorical nature of classification. As long as the shared similarities between groups are different from the fundamental characteristic defining the species or groups, they do not formally challenge the premise of a categorical classification itself. In the classification of psychoses, however, the psychotic, mood and cognitive symptoms, course and outcome, which are continuous across different diagnostic entities, are the very same attributes, defining categorical entities. This logical contradiction is perhaps the single most important reason fuelling the yet unresolved debate about how psychotic conditions should be classified. There are two solutions to this apparent contradiction. The first one is to abandon the categorical approach to the diagnosis of psychotic conditions and adopt a continuous/dimensional model. The second approach is to retain the classification of psychoses as a categorical one, but seek a better organizing principle that will allow for a logical interpretation and rationalization of the phenomena that are continuous over a broad range of current diagnostic groupings.

It has been recognized that new methods of investigation and recent advances in the field of molecular neuroscience, neuroimaging and genetics have the potential to reorganize considerably the classification of psychoses, and it has already been suggested that in time molecular genetic aetiology will replace clinical phenomenology as a basis of classification (Jablensky 1999b; Corrigan and Murray 1994; Kandel 1998). Again, our thinking of which level of complexity to choose as defining in a classification system and how to attempt to bridge the different layers of organismal structure and function could be directly informed by the process of conception and early development of the periodic table of the elements. In the periodic table the elements are arranged according to the electronic structure of their atoms

(Puddephatt and Monaghan 1986). In the years 1868-1870, when the table was first proposed by the Russian chemist Mendeleev the electronic structure of atoms had not been discovered yet. What was beginning to emerge at that time was the idea of periodic behaviour of the elements - i.e. when the elements are arranged in the order of increasing atomic weight, the physical and chemical properties of the eighth element resembled those of the first, those of the ninth were similar to those of the second, etc (the noble gases had not been discovered yet). Originally the periodic table was constructed by positioning the chemical elements in order of increasing atomic weights and grouping together the elements with similar physio-chemical properties. If the physical characteristics of the elements were not taken into consideration, the arrangement of elements from low to high atomic weight would have resulted in a linear sequence merely enlisting the elements without an appreciation of a fundamental attribute underlying chemical and physical periodicity. Also, it is quite apparent that the classification of the elements would have been different from the modern periodic table if the elements were classified solely on the basis of their physical and chemical properties (for example, elements would have been classified into solids, liquids and gases, based on their appearance, or into metals, non-metals and metalloids, based on their metallic properties). It appears that, despite the fact that the characteristics of the elements at an atomic level are reflected in their physical and chemical behaviour, the classification of elements based on both atomic weights and physio-chemical properties is different from and proven superior to the classifications of elements based upon either the atomic weight or the physical and chemical properties alone. It is generally believed that the electronic structure of atoms represents a 'natural' organizing concept of the chemical elements that renders the periodic table a 'natural' classification (Puddephatt and Monaghan 1986). But before this basic principal was recognized and almost universally validated, it was successfully approximated by taking simultaneously into account other characteristics at two different layers of elemental complexity, i.e. the fine structural atomic level accessible for investigation only to very sophisticated methodologies, and the physio-chemical or the elemental 'behavioural' level, accessible to observation by a naked human eye, or by relatively simple research tools.

The idea of attempting to understand an object or process by integrating information produced by different methods and levels of investigation is not new to medicine and psychiatry. In modern medical sciences it is ultimately desirable to understand how deficits or abnormalities at a genetic level are translated at a level of molecular, cell, organ and organismal physiology, or visa versa, what are the biological and genetic

correlates of a particular state of mind or cognitive-behavioural phenomenon. However, in practice, the approach to the diagnosis and classification of 'diseases' (including psychoses) is very different from the approach of classifying the chemical elements. The periodic table of the elements was created by simultaneous consideration of two levels of elemental complexity—i.e. atomic weights and physio-chemical properties. The groups (or the columns in the periodic table) represent clusters of elements with strong similarities in their physical properties and chemical behaviour. Within the groups the elements are not clumped together randomly, but are arranged in order of increasing atomic weight in a way that allows for the formation of a second axis within the table, i.e. the periods, or the rows in the table (Puddephatt and Monaghan 1986). This arrangement of elements in the periodic table permits the study of broad continuous trends in the chemical properties of the elements in terms of their position in the periodic table, rather than on individual compounds. Moreover, it has been recognized that "the vast expansion of knowledge about the elements and their compounds can only be comprehended in terms of the periodic table; it is no longer possible, or even desirable, to learn the properties of each chemical element or compound in isolation" (Puddephatt and Monaghan 1986, p.3). In contrast, the 'disease' entities of schizophrenia and bipolar illness along with the intermediate group of schizoaffective disorder are single-axis constructs, which are not further subjected to a simultaneous ordering along a second axis. Even though the currently accepted criteria for validating the 'disease' constructs call for supportive evidence from genetic and other laboratory studies, the information at the level of biology and clinical symptomatology has not been applied simultaneously for creating a true two-axial classification of psychoses in a way that atomic weight and chemical behaviour of the elements have been employed in drawing the periodic table.

As has been demonstrated by the periodic table of chemical elements, in matters with more than one level of structural and functional complexity, a classification approach based on at least two of these levels (or axes) is superior to classifications based on either level of complexity alone until a single universal 'natural' principal is identified and validated. Similarly, we believe that until such stable, 'natural' principal of classification of psychotic conditions is recognized, a classification approach that truly integrates information from at least two of the many layers of genetic, biological and phenomenological organization could be superior than an approach adopting organizing concepts along a single axis. Given the success of such an approach in the classification of elements, we believe that testing a classification

model of psychoses created simultaneously along two axes (or levels of individual structural and functional complexity) will be an exciting new direction for the near future of psychosis research that could ultimately resolve the debate and further refine our classification system.

Conclusions

1. There is a substantial, but not complete, correspondence between the clinical entities of dementia praecox and manic-depressive insanity introduced by Kraepelin in 1896 and the present-day diagnostic constructs of schizophrenia and bipolar illness (Jablensky et al. 1993; Jablensky and Woodbury 1995). Schizophrenia and bipolar illness have distinct features as well as share many similarities in their genetic predisposition, risk factors, brain pathology and neurophysiology, clinical symptomatology and treatment response (Wildenauer et al. 1999; Buka and Fan 1999; Jones and Tarrant 1999; Goldberg 1999; Pearlson 1999; Post 1999; Curtis et al. 2000). The similarities and differences between schizophrenia and bipolar illness have been extensively reviewed and debated, but cannot be interpreted unequivocally in order to prove or negate the validity of the two diagnostic concepts. It is equally possible to emphasize the differences between the two constructs, as it is to favour the similarities. It appears that the categorical entities of schizophrenia and bipolar illness are not as sharply delineated from one another as once believed and there is a range of other 'diagnostic groupings' such as schizoaffective disorder, cycloid psychoses and other atypical forms of psychotic illness that occupy intermediate grounds (Jablensky and Woodbury 1995). In essence, the overwhelming evidence from decades of clinical, epidemiological and biological research depicts a situation whereby the similarities and differences between schizophrenia and bipolar illness can only be recognized and enlisted, but cannot be adequately rationalized and understood in the context of the current classification algorithm of psychotic disorders.
2. The theoretical framework of purely dimensional approaches to psychiatric classification is not sufficiently developed, specific dimensional models of psychosis have not been systematically validated. Due to considerable limitations with respect to their clinical utility and applicability for genetic and other biological research, the dimensional models do not constitute a superior alternative to the categorical approach of psychotic illnesses.
3. An alternative strategy combining traditional categorical and dimensional approach (Woodbury et al. 1978; Woodbury and Manton 1982) is mathematically feasible and could be applied for the purpose of obtaining a disease definition and classification of mental

conditions, and for sampling of individuals for biological research (Manton et al. 1994; Jablensky 1997; Jablensky et al. 2002).

4. We propose a new conceptual model of classification of psychotic illnesses that is based on simultaneous ordering of individuals according to two levels of their biological and phenomenological complexity. This model is conceptually similar to the periodic table of the elements whereby objects grouped together on the basis of one organizing principle are at the same time subjected to ordering along a second axis. We expect that a true two-axis classification of psychotic illnesses will provide a basis for new sampling strategies for biological and clinical research that would be different from the sampling strategies derived from the existing classification models.

References

- Addington J, Addington D (1998) Facial affect recognition and information processing in schizophrenia and bipolar disorder. *Schizophr Res* 32: 171-181.
- Appelbaum PS, Robbins PC, Roth LH (1999) Dimensional approach to delusions: comparison across types and diagnoses. *Am J Psychiatry* 156: 1938-1943.
- Aylward EH, Roberts-Twillie JV, Barta PE, Kumar AJ, Harris GJ, Geer M, Peyser CE, Pearlson GD (1994) Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. *Am J Psychiatry* 151: 687-693.
- Banaschewski T, Schulz E, Martin M, Remschmidt H (2000) Cognitive functions and psychopathological symptoms in early-onset schizophrenia. *Eur Child Adolesc Psychiatry* 9: 11-20.
- Berrettini WH (2000) Genetics of psychiatric disease. *Annu Rev Med* 51: 465-479.
- Blackwood DH, He L, Morris SW, McLean A, Whitton C, Thomson M, Walker MT, Woodburn K, Sharp CM, Wright AF, Shibasaki Y, St Clair DM, Porteous DJ, Muir WJ (1996) A locus for bipolar affective disorder on chromosome 4p. *Nat Genet* 12: 427-430.
- Blazer D, Woodbury M, Hughes DC, George LK, Manton KG, Bachar JR, Fowler N (1989) A statistical analysis of the classification of depression in a mixed community and clinical sample. *J Affect Disord* 16: 11-20.
- Bleuler E (1911) *Dementia praecox oder die Gruppe der Schizophrenien*. Deuticke, Leipzig.
- Blouin JL, Dombroski BA, Nath SK, Lasseter VK, Wolyniec PS, Nestadt G, Thornquist M, Ullrich G, McGrath J, Kasch L, Lamacz M, Thomas MG, Gehrig C, Radhakrishna U, Snyder SE, Balk KG, Neufeld K, Swartz KL, DeMarchi N, Papadimitriou GN, Dikeos DG, Stefanis CN, Chakravarti A, Childs B, Pulver AE (1998) Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21. *Nat Genet* 20: 70-73.
- Botteron KN, Vannier MW, Geller B, Todd RD, Lee BC (1995) Preliminary study of magnetic resonance imaging characteristics in 8- to 16-year-olds with mania. *J Am Acad Child Adolesc Psychiatry* 34: 742-749.
- Brunet G, Cerlich B, Robert P, Dumas S, Souetre E, Darcourt G (1990) Open trial of a calcium antagonist, nimodipine, in acute mania. *Clin Neuropharmacol* 13: 224-228.

Brzustowicz LM, Honer WG, Chow EW, Little D, Hogan J, Hodgkinson K, Bassett AS (1999) Linkage of familial schizophrenia to chromosome 13q32. *Am J Hum Genet* 65: 1096-1103.

Brzustowicz LM, Hodgkinson KA, Chow EW, Honer WG, Bassett AS (2000) Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21-q22. *Science* 288: 678-682.

Buka SL, Fan AP (1999) Association of prenatal and perinatal complications with subsequent bipolar disorder and schizophrenia. *Schizophr Res* 39: 113-119.

Burnam MA, Hough RL, Escobar JJ, Karno M, Timbers DM, Telles CA, Locke BZ (1987) Six-month prevalence of specific psychiatric disorders among Mexican Americans and non-Hispanic whites in Los Angeles. *Arch Gen Psychiatry* 44: 687-694.

Campbell NA, Reece JB (2001) *Essential Biology*. Benjamin Cummings, San Francisco.

Cao Q, Martinez M, Zhang J, Sanders AR, Badner JA, Cravchik A, Markey CJ, Beshah E, Guroff JJ, Maxwell ME, Kazuba DM, Whiten R, Goldin LR, Gershon ES, Gejman PV (1997) Suggestive evidence for a schizophrenia susceptibility locus on chromosome 6q and a confirmation in an independent series of pedigrees. *Genomics* 43: 1-8.

Cassidy F, Pieper CF, Carroll BJ (2001) Subtypes of mania determined by grade of membership analysis. *Neuropsychopharmacology* 25: 373-383.

Cloninger CR (1989) Establishment of Diagnostic Validity in Psychiatric Illness: Robins and Guze's Method Revisited. In: Robins LN, Barrett JE (eds) *The Validity of Psychiatric Diagnosis*. Raven Press Ltd, New York, pp 9-18.

Coon H, Hoff M, Holik J, Hadley D, Fang N, Reimherr F, Wender P, Byerley W (1996) Analysis of chromosome 18 DNA markers in multiplex pedigrees with manic depression. *Biol Psychiatry* 39: 689-696.

Corder EH, Woodbury MA (1993) Genetic heterogeneity in Alzheimer's disease: a grade of membership analysis. *Genet Epidemiol* 10: 495-499.

Corder EH, Woodbury MA, Volkman I, Madsen DK, Bogdanovic N, Winblad B (2000) Density profiles of Alzheimer disease regional brain pathology for the huddinge brain bank: pattern recognition emulates and expands upon Braak staging. *Exp Gerontol* 35: 851-864.

Corder EH, Woodbury MA, Manton KG, Field LL (2001) Grade-of-membership sibpair linkage analysis maps IDDM11 to chromosome 14q24.3-q31. *Ann Hum Genet* 65: 387-394.

Corrigan RJ, Murray RM (1994) Twin concordance for congenital and adult-onset psychosis: a preliminary study of the validity of a novel classification of schizophrenia. *Acta Psychiatr Scand* 89: 142-145.

Crow TJ (1990) The continuum of psychosis and its genetic origins. The sixty-fifth Maudsley lecture. *Br J Psychiatry* 156: 788-797.

Crow TJ (1998) Precursors of psychosis as pointers to the Homo sapiens-specific mate recognition system of language. *Br J Psychiatry* 172: 289-290.

Crow TJ, Done DJ, Sacker A (1995) Childhood precursors of psychosis as clues to its evolutionary origins. *Eur Arch Psychiatry Clin Neurosci* 245: 61-69.

Curtis VA, van Os J, Murray RM (2000) The Kraepelinian dichotomy: evidence from developmental and neuroimaging studies. *J Neuropsychiatry Clin Neurosci* 12: 398-405.

Davidson J, Woodbury MA, Pelton S, Krishnan R (1988) A study of depressive typologies using grade of membership analysis. *Psychol Med* 18: 179-189.

Davidson JR, Woodbury MA, Zisook S, Giller EL, Jr. (1989) Classification of depression by grade of membership: a confirmation study. *Psychol Med* 19: 987-998.

Detera-Wadleigh SD, Badner JA, Goldin LR, Berrettini WH, Sanders AR, Rollins DY, Turner G, Moses T, Haerian H, Muniec D, Nurnberger JI, Jr., Gershon ES (1996) Affected-sib-pair analyses reveal support of prior evidence for a susceptibility locus for bipolar disorder, on 21q. *Am J Hum Genet* 58: 1279-1285.

Detera-Wadleigh SD, Badner JA, Berrettini WH, Yoshikawa T, Goldin LR, Turner G, Rollins DY, Moses T, Sanders AR, Karkera JD, Esterling LE, Zeng J, Ferraro TN, Guroff JJ, Kazuba D, Maxwell ME, Nurnberger JI, Jr., Gershon ES (1999) A high-density genome scan detects evidence for a bipolar-disorder susceptibility locus on 13q32 and other potential loci on 1q32 and 18p11.2. *Proc Natl Acad Sci U S A* 96: 5604-5609.

Done DJ, Crow TJ, Johnstone EC, Sacker A (1994) Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. *BMJ* 309: 699-703.

Egeland JA (1988) A genetic study of manic-depressive disorder among the old order Amish of Pennsylvania. *Pharmacopsychiatry* 21: 74-75.

El Badri SM, Ashton CH, Moore PB, Marsh VR, Ferrier IN (2001) Electrophysiological and cognitive function in young euthymic patients with bipolar affective disorder. *Bipolar Disord* 3: 79-87.

Ewald H, Degn B, Mors O, Kruse TA (1998a) Significant linkage between bipolar affective disorder and chromosome 12q24. *Psychiatr Genet* 8: 131-140.

Ewald H, Degn B, Mors O, Kruse TA (1998b) Support for the possible locus on chromosome 4p16 for bipolar affective disorder. *Mol Psychiatry* 3: 442-448.

Faraone SV, Matise T, Svrakic D, Pepple J, Malaspina D, Suarez B, Hampe C, Zambuto CT, Schmitt K, Meyer J, Markel P, Lee H, Harkavy FJ, Kaufmann C, Cloninger CR, Tsuang MT (1998) Genome scan of European-American schizophrenia pedigrees: results of the NIMH Genetics Initiative and Millennium Consortium. *Am J Med Genet* 81: 290-295.

Foroud T, Castelluccio PF, Koller DL, Edenberg HJ, Miller M, Bowman E, Rau NL, Smiley C, Rice JP, Goate A, Armstrong C, Bierut LJ, Reich T, Detera-Wadleigh SD, Goldin LR, Badner JA, Guroff JJ, Gershon ES, McMahon FJ, Simpson S, MacKinnon D, McInnis M, Stine OC, DePaulo JR, Blehar MC, Nurnberger JI, Jr. (2000) Suggestive evidence of a locus on chromosome 10p using the NIMH genetics initiative bipolar affective disorder pedigrees. *Am J Med Genet* 96: 18-23.

Freimer NB, Reus VI, Escamilla MA, McInnes LA, Spesny M, Leon P, Service SK, Smith LB, Silva S, Rojas E, Gallegos A, Meza L, Fournier E, Baharloo S, Blankenship K, Tyler DJ, Batki S, Vinogradov S, Weissenbach J, Barondes SH, Sandkuijl LA (1996) Genetic mapping using haplotype, association and linkage methods suggests a locus for severe bipolar disorder (BPI) at 18q22-q23. *Nat Genet* 12: 436-441.

Frye MA, Ketter TA, Altshuler LL, Denicoff K, Dunn RT, Kimbrell TA, Cora-Locatelli G, Post RM (1998) Clozapine in bipolar disorder: treatment implications for other atypical antipsychotics. *J Affect Disord* 48: 91-104.

Torrey EF (1999) Epidemiological comparison of schizophrenia and bipolar disorder. *Schizophr Res* 39: 101-106.

Goldberg TE (1999) Some fairly obvious distinctions between schizophrenia and bipolar disorder. *Schizophr Res* 39: 127-132.

Goodwin FK, Jamison KR (1990) Manic-depressive illness. Oxford University Press, New York.

Gurling HM, Kalsi G, Brynjolfsson J, Sigmundsson T, Sherrington R, Mankoo BS, Read T, Murphy P, Blaveri E, McQuillin A, Petursson H, Curtis D (2001) Genomewide genetic linkage analysis confirms the presence of susceptibility loci for schizophrenia, on chromosomes 1q32.2, 5q33.2, and 8p21-22 and provides support for linkage to schizophrenia, on chromosomes 11q23.3-24 and 20q12.1-11.23. *Am J Hum Genet* 68: 661-673.

Hawkins KA, Hoffman RE, Quinlan DM, Rakfeldt J, Docherty NM, Sledge WH (1997) Cognition, negative symptoms, and diagnosis:

a comparison of schizophrenic, bipolar, and control samples. *J Neuropsychiatry Clin Neurosci* 9: 81-89.

Jablensky A (1995) Kraepelin's legacy: paradigm or pitfall for modern psychiatry? *Eur Arch Psychiatry Clin Neurosci* 245: 186-188.

Jablensky A (1997) The 100-year epidemiology of schizophrenia. *Schizophr Res* 28: 111-125.

Jablensky A (1999a) The conflict of the nosologists: views on schizophrenia and manic-depressive illness in the early part of the 20th century. *Schizophr Res* 39: 95-100.

Jablensky A (1999b) The nature of psychiatric classification: issues beyond ICD-10 and DSM-IV. *Aust N Z J Psychiatry* 33: 137-144.

Jablensky A (2000) Epidemiology of schizophrenia: the global burden of disease and disability. *Eur Arch Psychiatry Clin Neurosci* 250: 274-285.

Jablensky A, Woodbury MA (1995) Dementia praecox and manic-depressive insanity in 1908: a Grade of Membership analysis of the Kraepelinian dichotomy. *Eur Arch Psychiatry Clin Neurosci* 245: 202-209.

Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, Day R, Bertelsen A (1992) Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychol Med Monogr Suppl* 20: 1-97.

Jablensky A, Hugler H, Von Cranach M, Kalinov K (1993) Kraepelin revisited: a reassessment and statistical analysis of dementia praecox and manic-depressive insanity in 1908. *Psychol Med* 23: 843-858.

Jablensky A, Hallmayer J, Michie PT, Kent A (2002) Linkage analysis in schizophrenia using a composite neurocognitive endophenotype. *Schizophr Res* 53: 24.

Johnstone EC, Crow TJ, Frith CD, Husband J, Kreef L (1976) Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet* 2: 924-926.

Jones P, Rodgers B, Murray R, Marmot M (1994) Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet* 344: 1398-1402.

Jones PB, Tarrant CJ (1999) Specificity of developmental precursors to schizophrenia and affective disorders. *Schizophr Res* 39: 121-125.

Jordan BK, Swartz MS, George LK, Woodbury MA, Blazer DG (1989) Antisocial and related disorders in a southern community. An application of grade of membership analysis. *J Nerv Ment Dis* 177: 529-541.

Kandel ER (1998) A new intellectual framework for psychiatry. *Am J Psychiatry* 155: 457-469.

Karakula H, Grzywa A (1999) Dimensions of psychopathology in paranoid schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 249: 247-255.

Kelsoe JR, Spence MA, Loetscher E, Foguet M, Sadovnick AD, Remick RA, Flodman P, Khristich J, Mroczkowski-Parker Z, Brown JL, Masser D, Ungerleider S, Rapaport MH, Wishart WL, Luebbert H (2001) A genome survey indicates a possible susceptibility locus for bipolar disorder on chromosome 22. *Proc Natl Acad Sci U S A* 98: 585-590.

Kendler KS, Hays P (1983) Schizophrenia subdivided by the family history of affective disorder. A comparison of symptomatology and course of illness. *Arch Gen Psychiatry* 40: 951-955.

Kendler KS, Tsuang MT (1988) Outcome and familial psychopathology in schizophrenia. *Arch Gen Psychiatry* 45: 338-346.

Kendler KS, MacLean CJ, O'Neill FA, Burke J, Murphy B, Duke F, Shinkwin R, Easter SM, Webb BT, Zhang J, Walsh D, Straub RE (1996) Evidence for a schizophrenia vulnerability locus on chromosome 8p in the Irish Study of High-Density Schizophrenia

Families. *Am J Psychiatry* 153: 1534-1540.

Kraepelin E (1896) *Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. Fünfte, vollständige umgearbeitete Auflage* Barth, Leipzig.

Kraepelin E (1920) *Der Erscheinungsformen der Irreseins. Zeitschrift für Gesamte Neurologie u Psychiatrie* 62: 1-29.

Kremen WS, Seidman LJ, Faraone SV, Tsuang MT (2001) Intelligence quotient and neuropsychological profiles in patients with schizophrenia and in normal volunteers. *Biol Psychiatry* 50: 453-462.

Kwok JB, Adams LJ, Salmon JA, Donald JA, Mitchell PB, Schofield PR (1999) Nonparametric simulation-based statistical analyses for bipolar affective disorder locus on chromosome 21q22.3. *Am J Med Genet* 88: 99-102.

Levinson DF, Holmans P, Straub RE, Owen MJ, Wildenauer DB, Gejman PV, Pulver AE, Laurent C, Kendler KS, Walsh D, Norton N, Williams NM, Schwab SG, Lerer B, Mowry BJ, Sanders AR, Antonarakis SE, Blouin JL, DeLeuze JF, Mallet J (2000) Multicentre linkage study of schizophrenia candidate regions on chromosomes 5q, 6q, 10p, and 13q: schizophrenia linkage collaborative group III. *Am J Hum Genet* 67: 652-663.

Manton KG, Korten A, Woodbury MA, Anker M, Jablensky A (1994) Symptom profiles of psychiatric disorders based on graded disease classes: an illustration using data from the WHO International Pilot Study of Schizophrenia. *Psychol Med* 24: 133-144.

Martinez M, Goldin LR, Cao Q, Zhang J, Sanders AR, Nancarrow DJ, Taylor JM, Levinson DF, Kirby A, Crowe RR, Andreasen NC, Black DW, Silverman JM, Lennon DP, Nertney DA, Brown DM, Mowry BJ, Gershon ES, Gejman PV (1999) Follow-up study on a susceptibility locus for schizophrenia on chromosome 6q. *Am J Med Genet* 88: 337-343.

McDonald WM, Krishnan KR, Doraiswamy PM, Blazer DG (1991) Occurrence of subcortical hyperintensities in elderly subjects with mania. *Psychiatry Res* 40: 211-220.

McInnes LA, Escamilla MA, Service SK, Reus VI, Leon P, Silva S, Rojas E, Spesny M, Baharloo S, Blankenship K, Peterson A, Tyler D, Shimayoshi N, Tobey C, Batki S, Vinogradov S, Meza L, Gallegos A, Fournier E, Smith LB, Barondes SH, Sandkuijl LA, Freimer NB (1996) A complete genome screen for genes predisposing to severe bipolar disorder in two Costa Rican pedigrees. *Proc Natl Acad Sci U S A* 93: 13060-13065.

McMahon FJ, Hopkins PJ, Xu J, McInnis MG, Shaw S, Cardon L, Simpson SG, MacKinnon DF, Stine OC, Sherrington R, Meyers DA, DePaulo JR (1997) Linkage of bipolar affective disorder to chromosome 18 markers in a new pedigree series. *Am J Hum Genet* 61: 1397-1404.

Moises HW, Yang L, Kristbjarnarson H, Wiese C, Byerley W, Macchiardi F, Arolt V, Blackwood D, Liu X, Sjogren B (1995) An international two-stage genome-wide search for schizophrenia susceptibility genes. *Nat Genet* 11: 321-324.

Morissette J, Villeneuve A, Bordeleau L, Rochette D, Laberge C, Gagne B, Laprise C, Bouchard G, Plante M, Gobeil L, Shink E, Weissenbach J, Barden N (1999) Genome-wide search for linkage of bipolar affective disorders in a very large pedigree derived from a homogeneous population in Quebec points to a locus of major effect on chromosome 12q23-q24. *Am J Med Genet* 88: 567-587.

Murray RM, Lewis SW, Reveley AM (1985) Towards an aetiological classification of schizophrenia. *Lancet* 1: 1023-1026.

Nurnberg HG, Woodbury MA, Bogenschutz MP (1999) A mathematical typology analysis of DSM-III-R personality disorder classification: grade of membership technique. *Compr Psychiatry* 40: 61-71.

Oulis P, Lykouras L, Gournellis R, Mamounas J, Hatzimanolis J, Christodoulou GN (2000) Clinical features of delusional beliefs in schizophrenic and unipolar mood disorders: a comparative study. *Psychopathology* 33: 310-313.

Pazzaglia PJ, Post RM, Ketter TA, George MS, Marangell LB (1993)

Preliminary controlled trial of nimodipine in ultra-rapid cycling affective dysregulation. *Psychiatry Res* 49: 257-272.

Pazzaglia PJ, Post RM, Ketter TA, Callahan AM, Marangell LB, Frye MA, George MS, Kimbrell TA, Leverich GS, Cora-Locatelli G, Luckenbaugh D (1998) Nimodipine monotherapy and carbamazepine augmentation in patients with refractory recurrent affective illness. *J Clin Psychopharmacol* 18: 404-413.

Pearlson GD (1999) Structural and functional brain changes in bipolar disorder: a selective review. *Schizophr Res* 39: 133-140.

Pearlson GD, Veroff AE (1981) Computerised tomographic scan changes in manic-depressive illness. *Lancet* 2: 470.

Pekkarinen P, Terwilliger J, Bredbacka PE, Lonqvist J, Peltonen L (1995) Evidence of a predisposing locus to bipolar disorder on Xq24-q27.1 in an extended Finnish pedigree. *Genome Res* 5: 105-115.

Piccinelli M, Rucci P, Ustun B, Simon G (1999) Typologies of anxiety, depression and somatization symptoms among primary care attenders with no formal mental disorder. *Psychol Med* 29: 677-688.

Pickar D, Wolkowitz OM, Doran AR, Labarca R, Roy A, Breier A, Narang PK (1987) Clinical and biochemical effects of verapamil administration to schizophrenic patients. *Arch Gen Psychiatry* 44: 113-118.

Post RM (1999) Comparative pharmacology of bipolar disorder and schizophrenia. *Schizophr Res* 39: 153-158.

Puddephatt RJ, Monaghan PK (1986) *The periodic table of the elements*. Clarendon Press, Oxford; Oxford University Press, New York.

Robins E, Guze SB (1970) Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry* 126: 983-987.

Sartorius N, Ustun TB, Korten A, Cooper JE, van Drimmelen J (1995) Progress toward achieving a common language in psychiatry, II: Results from the international field trials of the ICD-10 diagnostic criteria for research for mental and behavioural disorders. *Am J Psychiatry* 152: 1427-1437.

Schwab SG, Albus M, Hallmayer J, Honig S, Borrmann M, Lichtermann D, Ebstein RP, Ackenheil M, Lerer B, Risch N (1995) Evaluation of a susceptibility gene for schizophrenia on chromosome 6p by multipoint affected sib-pair linkage analysis. *Nat Genet* 11: 325-327.

Schwab SG, Hallmayer J, Albus M, Lerer B, Hanses C, Kanyas K, Segman R, Borrmann M, Dreikorn B, Lichtermann D, Rietschel M, Trixler M, Maier W, Wildenauer DB (1998) Further evidence for a susceptibility locus on chromosome 10p14-p11 in 72 families with schizophrenia by nonparametric linkage analysis. *Am J Med Genet* 81: 302-307.

Seidman LJ, Kremen WS, Koren D, Faraone SV, Goldstein JM, Tsuang MT (2002) A comparative profile analysis of neuropsychological functioning in patients with schizophrenia and bipolar psychoses. *Schizophr Res* 53: 31-44.

Sheldrick C, Jablensky A, Sartorius N, Shepherd M (1977) Schizophrenia succeeded by affective illness; catamnestic study and statistical enquiry. *Psychol Med* 7: 619-624.

Shenton ME, Dickey CC, Frumin M, McCarley RW (2001) A review of MRI findings in schizophrenia. *Schizophr Res* 49: 1-52.

Smyth C, Kalsi G, Curtis D, Brynjolfsson J, O'Neill J, Rifkin L, Moloney E, Murphy P, Petursson H, Gurling H (1997) Two-locus admixture linkage analysis of bipolar and unipolar affective disorder supports the presence of susceptibility loci on chromosomes 11p15 and 21q22. *Genomics* 39: 271-278.

Stine OC, Xu J, Koskela R, McMahon FJ, Gschwend M, Friddle C, Clark CD, McInnis MG, Simpson SG, Breschel TS (1995) Evidence for linkage of bipolar disorder to chromosome 18 with a parent-of-origin effect. *Am J Hum Genet* 57: 1384-1394.

Straub RE, Lehner T, Luo Y, Loth JE, Shao W, Sharpe L, Alexander JR, Das K, Simon R, Fieve RR (1994) A possible vulnerability locus for bipolar affective disorder on chromosome 21q22.3. *Nat Genet* 8: 291-296.

Straub RE, MacLean CJ, Walsh D, Kendler KS (1996) Support for schizophrenia vulnerability loci on chromosomes 6p and 8p from Irish families. *Cold Spring Harb Symp Quant Biol* 61: 823-833.

Swartz MS, Blazer DG, Woodbury MA, George LK, Manton KG (1987) A study of somatization disorder in a community population utilizing grade of membership analysis. *Psychiatr Dev* 5: 219-237.

Torrey EF (1999) Epidemiological comparison of schizophrenia and bipolar disorder. *Schizophr Res* 39: 101-106.

Torrey EF, Knable MB (1999) Are schizophrenia and bipolar disorder one disease or two? *Schizophr Res* 39: 93-94.

Valles V, van Os J, Guillamat R, Gutierrez B, Campillo M, Gento P, Fananas L (2000) Increased morbid risk for schizophrenia in families of in-patients with bipolar illness. *Schizophr Res* 42: 83-90.

van Os J, Fahy TA, Jones P, Harvey I, Sham P, Lewis S, Bebbington P, Toone B, Williams M, Murray R (1996) Psychopathological syndromes in the functional psychoses: associations with course and outcome. *Psychol Med* 26: 161-176.

van Os J, Jones P, Lewis G, Wadsworth M, Murray R (1997) Developmental precursors of affective illness in a general population birth cohort. *Arch Gen Psychiatry* 54: 625-631.

Wang S, Sun CE, Walczak CA, Ziegler JS, Kipps BR, Goldin LR, Diehl SR (1995) Evidence for a susceptibility locus for schizophrenia on chromosome 6pter-p22. *Nat Genet* 10: 41-46.

Wiersma D, Nienhuis FJ, Slooff CJ, Giel R (1998) Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophr Bull* 24: 75-85.

Wildenauer DB, Schwab SG, Maier W, Detera-Wadleigh SD (1999) Do schizophrenia and affective disorder share susceptibility genes? *Schizophr Res* 39: 107-111.

Woodbury MA, Manton KG (1982) A new procedure for analysis of medical classification. *Methods Inf Med* 21: 210-220.

Woodbury MA, Clive J, Garson A, Jr. (1978) Mathematical typology: a grade of membership technique for obtaining disease definition. *Comput Biomed Res* 11: 277-298.

Three Cases of Zolpidem Dependence Treated with Fluoxetine: The Serotonin Hypothesis

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Summary

Zolpidem is an imidazopyridine hypnotic that is believed to act selectively at α_1 subunit-containing gamma-aminobutyric acid type A ($GABA_A$) receptors and thus to have minimal abuse and dependence potential. We present three cases of zolpidem abuse and dependence in which the drug was used not for sedation but for stimulation and anxiolysis. All of the patients were treated with fluoxetine (a selective serotonin reuptake inhibitor) and managed to discontinue the abuse and remain abstinent from the drug. The efficacy of this kind of medication on the abuse of a $GABA_A$ agonist, in this case dependence on zolpidem, leads to a serotonergic and $GABA_A$ system interaction hypothesis.

Key words: zolpidem, abuse, dependence, fluoxetine.

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Introduction

Zolpidem is a gamma-aminobutyric acid (GABA) agonist that binds on the benzodiazepine site of the pentameric receptor (Langtry and Benfield 1990; Holm and Goa 2000). It is proposed to act selectively at α_1 subunit-containing benzodiazepine receptors and thus to have a low dependence potential (Benavides et al. 1990; Korpi et al. 1997; Lancel 1999; Mitler 2000). Nevertheless, there are a considerable number of cases reported in the literature of zolpidem abuse and dependence (Gericke and Ludolph 1994; Ravishankar and Carnwath 1998; Courtet et al. 1999; Aragona 2000; Golden and Vagnoni 2000). We will present three cases of zolpidem abuse in which high doses of the drug were used not to treat insomnia (the initial reason for prescription of zolpidem) but to induce anxiolysis, euphoria and stimulation in order to cope with everyday problems.

Case reports

• Case 1

A 30-year-old, single, wealthy male presented at the Drug-Free Outpatient Drug Addiction Department of Athens University Psychiatric Clinic (ATHENA) with a history of abuse and dependence on cocaine. He had no prior family or personal medical record of drug abuse, but had been smoking cigarettes since the age of 18. His history of abuse started with the use of cocaine when he was 20 years old. From that time until the age of 25 he used the substance occasionally for recreational reasons at parties, always by inhalation. The patient had no criminal record and used no other drugs.

A few years before the patient presented at the clinic his mother had developed malignant disease and died after a short period of time. At that time, the patient manifested symptoms that fulfilled the criteria for a diagnosis of dysthymic disorder. His use of cocaine became systematic (intensified abuser), and within the next two months he inhaled up to 5 g daily. Because of the intense craving that followed the substance use, the patient started to ingest zolpidem tablets in order to calm down. Zolpidem was prescribed by

a general practitioner for the treatment of insomnia resulting from the cocaine abuse.

One year before presenting at the clinic, the patient became a pathological gambler, and through cocaine abuse gambled a large amount of money on the international stock market via the internet. He consumed 3-4 g of cocaine daily in several doses. Two to three hours after the last inhalation he ingested three to four tablets of zolpidem, reaching 20-30 tablets (200-300 mg) per night. The patient claimed that he never used zolpidem as a sedative drug, but as a means of progressive reduction of his cocaine craving. He pointed out that after using zolpidem he became more excited, hyperactive, logorrhic and euphoric, and often exhibited childish behaviour. Moreover, he had memory blanks regarding events which took place under the influence of zolpidem.

This situation lasted for about a year until he sought the help of a specialized psychiatrist. With the doctor's help he gradually discontinued both cocaine and zolpidem, without demonstrating any specific withdrawal symptoms, apart from hypersomnia, hyperphagia and depression, all of which are induced by cocaine interruption. The symptoms were treated with cognitive-behavioural psychotherapy (CBT) and medication (fluoxetine 20 mg twice daily). CBT commenced one month after the initiation of fluoxetine treatment and was offered to the patient for two months. After eight months of follow-up observation, the patient reports total abstinence from the substances, normothymia and says that he is adapting well. He is still receiving fluoxetine, and his abstinence from the drugs is confirmed twice weekly by urine analysis.

• Case 2

A 35-year-old, divorced, unemployed woman with no criminal record or history of other substance abuse contacted the Drug Clinic with a zolpidem abuse problem. She had a history of onychophagia, eating disorders and impulsive suicide attempts. A year before presenting at the clinic, the patient developed anxiety, dysphoric mood and intense initial insomnia due to family and financial problems. She took zolpidem, and after a month she was taking 10-15 tablets per day in two to three doses. She was using zolpidem for stimulation purposes in order to face her daily activities. The substance intoxication brought her energy, euphoria, mild dysarthria, hyperactivity, impulsive behaviour and sometimes anterograde memory impairment. The patient followed the Drug Clinic's treatment programme, abruptly stopped taking the drug without experiencing any withdrawal symptoms and started therapy with fluoxetine 20 mg twice daily. The programme is an out-patient drug-free (without using any substitute substances) drug addiction programme in which

cognitive-behavioural psychotherapy (CBT) is used as the basic technique. Occasionally, in some cases of minor and transient psychopathology (depressive-like, anxiety-like symptomatology), CBT is combined with pharmacotherapy for a short period of time. After six months the patient is still abstinent from zolpidem.

• Case 3

A 42-year-old, divorced male physician with no history of a somatic or psychiatric disorder or of substance abuse and without a criminal record was hospitalised in the Psychiatric Department of Eginition University Hospital of Athens with a zolpidem dependence problem.

He was extrovert, sociable and sensitive and, at the age of 32, demonstrated progressive initial insomnia without any other psychopathology. He started therapy with 10 mg zolpidem, prescribed by a doctor, and a few months later was consuming 30-40 mg per night. He would quite often lose control and ingest up to 30 tablets (300 mgs). The substance abuse brought him euphoria, a feeling of well-being, made him capable of dealing with his everyday problems and helped him to keep up with the demands of his profession. He frequently presented confusion, memory blanks and amnesia of variable duration. Over the past three years he had been taking 600 mgs zolpidem daily in five to six doses in order to maintain his everyday feeling of well-being. Under the drug intoxication he demonstrated hyperactivity, euphoria and memory blanks. When he attempted to discontinue the drug abruptly he developed confusion, amnesia and occasionally (once or twice) epileptic seizures (he was once hospitalised in an intensive care unit due to *status epilepticus*). He hardly ever discontinued the drug without any withdrawal symptoms.

Immediately after his admission to the University Psychiatric Department zolpidem use was discontinued and 20 mgs fluoxetine administered three times daily. Although fluoxetine has a long half-life, it was administered three times daily according to the patient's wishes (as mentioned above, he was a physician). Zolpidem was abruptly discontinued, also in line with the patient's wishes, because in the past he had attempted many times (more than ten) to stop abruptly the use of the drug without having seizures. The patient had no withdrawal symptoms and after one month's therapy is completely asymptomatic.

Discussion

We have presented three cases of zolpidem dependence in which the patients were prescribed the drug by their doctor. They were being treated for insomnia and given the drug for sedation. It is remarkable that the patients

differed considerably yet developed a similar pattern of abuse.

The first case is a male, non-working, wealthy patient with a history of substance abuse (cocaine) who was given zolpidem in order to calm down and reduce the craving for cocaine. The second case is an unemployed female with no history of substance abuse, who suffered from initial insomnia, anxiety and dysphoric mood in the context of family and financial problems. The third case is a sociable, successful physician with no history of psychiatric disorders or substance abuse and with no psychopathology apart from his initial insomnia.

Nevertheless, in all cases the drug was used not for sedation but to achieve euphoria and stimulation. Through the substance abuse the patients became energetic, excited and euphoric. They were able to cope with their anxiety and deal with everyday problems.

The patients followed the treatment programme and managed to discontinue the abuse without having any withdrawal symptoms. All of our cases were tested with the Hamilton-Anxiety and Hamilton-Depression scales and demonstrated low scores (between 4 and 8). Two of the patients were treated with 40 mgs fluoxetine daily, and the third patient with 60 mgs daily, doses also recommended for depressive and anxiety disorders. For the time being they are still abstinent under medication with fluoxetine.

Is it possible that control of the depressive and anxiety symptoms alone kept our patients away from continuing to abuse the substance? Zolpidem is supposed to interact only with the GABAergic system and, moreover, it was proposed to demonstrate selectivity for the α_1 GABA_A subunits. On the other hand, fluoxetine is a selective serotonin reuptake inhibitor (SSRI) and supposed to have a relatively specific effect on this monoamine system, lacking antagonism and affinity for many other receptors (Kelsey and Nemeroff 2000; Heninger 2000).

However, studies have revealed that zolpidem reduces serotonin synthesis in the hippocampus, striatum and frontal cortex (Scatton et al. 1986). Moreover, activation of presynaptic serotonin receptors is found to inhibit synaptic GABA release (Koyama et al. 1999). It is known that the serotonergic system lacks functional specialization, and interacts with the cholinergic, glutamergic, dopaminergic and GABAergic systems, playing a role in a great variety of behaviours (Buhot et al. 2000).

Comparing zolpidem abuse with alcohol abuse, using the possible involvement of the same neurotransmitter (GABA) as a common pathway, and taking into consideration the reduced serotonin function and the beneficial activity of

SSRIs on alcoholics (Nutt 1996), we could hypothesize a similar beneficial action of such a drug, in this case fluoxetine, in treating the zolpidem abuse of our patients.

Taking into consideration the vast complexity of neurons and neurotransmitter interaction it is possibly an oversimplification to claim that zolpidem's effect as a GABAergic agonist reduced the activity of the serotonergic system that was compensated by decreasing the reuptake of serotonin in the treatment of zolpidem abuse. Nevertheless, it is an interesting hypothesis which could partially explain the positive response of our patients to fluoxetine and their excellent course to date.

References

- Aragona M (2000) Abuse, dependence, and epileptic seizures after zolpidem withdrawal: Review and case report. *Clin Neuropharmacol* 23: 281-283.
- Benavides J, Depoortere H, Sanger D, Perrault G, Arbilla S, Langer SZ, Zivkovic B, Scatton B (1990) Un domaine spécifique (site ω_1) du récepteur GABAA pourrait être impliqué dans les effets hypnotiques du zolpidem. *L'Encéphale* 16: 13-22.
- Buhot M, Martin S, Segu L (2000) Role of serotonin in memory impairment. *Ann Med* 32: 210-221.
- Courtet P, Pignay V, Castelnaud D, Boulenger JP (1999) Abus et dépendance au zolpidem: à propos de sept cas. *L'Encéphale* 25: 652-657.
- Gericke C, Ludolph A (1994) Chronic abuse of zolpidem. *JAMA* 272: 1721-1722.
- Golden S, Vagnoni C (2000) Zolpidem dependence and prescription fraud. *Am J Addict* 9: 96-97.
- Heninger G (2000) Antidepressants. *New Oxford Textbook of Psychiatry*. Oxford University Press, New York, pp 1293-1305.
- Holm K, Goa K (2000) Zolpidem An update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs* 59: 865-889.
- Kelsey J, Nemeroff C (2000) Fluoxetine. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. Lippincott Williams & Wilkins, Philadelphia, pp 2438-2444.
- Korpi E, Mattila M, Wisden W, Lüddens H (1997) GABA_A receptor subtypes: Clinical efficacy and selectivity of benzodiazepine site ligands. *Ann Med* 29: 275-282.
- Koyama S, Kubo C, Rhee JS, Akaike N (1999) Presynaptic serotonergic inhibition of GABAergic synaptic transmission in mechanically dissociated rat basolateral amygdala neurons. *J Physiol* 518: 525-538.
- Lancel M (1999) Role of GABA_A receptors in the regulation of sleep: Initial sleep responses to peripherally administered modulators and agonists. *Sleep* 22: 33-41.
- Langtry H, Benfield P (1990) Zolpidem A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. *Drugs* 40: 291-313.
- Mitler M (2000) Nonselective and selective benzodiazepine receptor agonists – where are we today? *Sleep* 23 (Suppl 1): 39-46.

Nutt D (1996) Addiction: brain mechanisms and their treatment implications. *Lancet* 347: 31-36.

Ravishankar A, Carnwath T (1998) Zolpidem tolerance and dependence — two case reports. *J Psychopharmacol* 12: 103-104.

Scatton B, Claustre Y, Dennis T, Nishikawa T (1986) Zolpidem, a novel nonbenzodiazepine hypnotic. II. Effects on cerebellar cGMP and cerebral monoamines. *J Pharm Exp Ther* 237: 659-665.

Erratum: The title of the Editorial by Carlos R. Hojaj published in the January issue should read "A Psychopathological Marker for Biological Psychiatry" [*World J Biol Psychiatry* (2003) 4, 2-3]. The Journal regrets the error.

Instructions to Authors

Papers must be written in standard and grammatical English and should present new results as well as be of scientific value. Contributions will be considered for the following categories:

Reviews/Mini-reviews
Original investigations/Summaries of original research
Brief reports
Viewpoints
Case reports/Case series
Meet the Expert
Letters to the editors
News from the pharmaceutical industry
Book reviews
Invitations/Announcements

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The subject matter should be defined in a few sentences and earlier work on the subject referred to by citing recent bibliographies (in monographs, handbooks, etc). The reader should be able to follow the method by which the results were obtained, but there is no value in detailed descriptions unless they constitute a genuine innovation.

Mere confirmation of established findings is to be strictly avoided. Experiments with no significant results, if included at all, should be dealt with only briefly. Case histories and examination reports should be included only if necessary for defining the subject matter and are to be presented as concisely as possible.

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Brain WR (1958) The physiological basis of consciousness. A critical review. *Brain* 81: 426-455.

Kuhlenbeck H (1954) The human diencephalon. A summary of development, structure, function and pathology. Karger, Basel.

Teuber HL (1964) The riddle of frontal lobe function in man. In: Warren T, Akert CH (eds) *The frontal and granular cortex and behavior*. McGraw-Hill, New York, pp 252-271.

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