Partial agonists in schizophrenia

The editorial by Bolonna & Kerwin (2005) is both timely and important. The authors succinctly present the case for the use of partial agonists of dopamine receptors, concluding that ‘the reviewed evidence suggests a promising future for dopamine receptor partial agonists’. While this is arguably true on the basis of the evidence presented, theoretical and empirical concerns regarding the use of these medications remain.

The introduction of aripiprazole on an individual patient level may prove problematic (DeQuardo, 2004; Ramaswamy et al, 2004). Although effective switching strategies from atypical agents to aripiprazole have been described, a number of reports of worsening psychosis following the introduction of aripiprazole (DeQuardo, 2004; Ramaswamy et al, 2004) have been published. While these cases may be accounted for by unrelated illness relapse, other theoretical explanations should be considered. Up-regulation of dopamine receptors is well recognised during treatment with neuroleptics, and results in supersensitivity to dopamine at the sites of receptor blockade. This has led to the concept of a neuroleptic-induced supersensitivity psychosis (Steiner et al, 1990) wherein up-regulation effectively outstrips receptor blockade with emergent psychosis resistant to treatment. Supersensitivity could explain cases of psychosis developing with aripiprazole. Cessation of an antagonist with subsequent introduction of a partial agonist could result in a net excess of neurotransmission due to over-stimulation of a supersensitive system (despite the partial agonist demonstrating sub-maximal stimulation in normal systems). The high receptor affinity of partial agonists may make this situation difficult to treat, as few drugs are likely to be able to displace these agents from receptor complexes. Drugs that can displace partial agonists run the risk of negating the therapeutic effects of stabilisation of the dopaminergic system in schizophrenia, perhaps most importantly at times of relapse when patients are likely to receive ‘as required’ doses of potent D2 antagonists.

While empirical evidence largely supports the primary efficacy of these agents (DeLeon et al, 2004), clinical experience of partial agonists is in its infancy. Good-quality data from naturalistic studies are required to establish the effectiveness of these drugs, but in the meantime we call for post-marketing surveillance to quantify the scale of the problem of cross-titration.

**Correspondence**

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**Partial agonists in schizophrenia**

The editorial by Bolonna & Kerwin (2005) is both timely and important. The authors succinctly present the case for the use of partial agonists of dopamine receptors, concluding that ‘the reviewed evidence suggests a promising future for dopamine receptor partial agonists’. While this is arguably true on the basis of the evidence presented, theoretical and empirical concerns regarding the use of these medications remain.

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**Suicide in prisons**

On 13 January 2004 Dr Harold Shipman, a doctor convicted of murder, was found dead in his prison cell, following apparent self-hanging. Subsequent media reports tended to give considerable detail about the apparent circumstances of his death.

In 1999 there were, on average, 1.8 self-inflicted deaths per week in prisons in England and Wales, yielding a rate of 0.3 per 10 000 prisoners per week (HM Prison Service, 2001). Preliminary data for 2003 are similar, indicating 1.8 apparently self-inflicted deaths (inquests pending) per week (Seean, 2004). In the week following the death of Dr Shipman, five apparently self-inflicted deaths (inquests pending) were reported in prisons in England and Wales (HM Prison Service Safer Custody Group, personal communication, 2004); this apparent peak, however, is similar to that in a comparable week in January 2003.

In Irish prisons, there were nine apparently self-inflicted deaths (inquests pending) between January 2000 and April 2003, yielding a rate of 0.2 per 10 000 prisoners per week (Bresnihan, 2003). In the week following the death of Dr Shipman, there were two apparently self-inflicted deaths (inquests pending; Brady, 2004), yielding an increased rate of 6.4 per 10 000 prisoners that week (Poisson distribution $P=0.0018$). While caution must be exercised when interpreting data about rare events, we note the less believe these data merit explanation.

At a population level, one possible explanation relates to prisoners’ average ‘dose’ of exposure to detailed, graphic media coverage of suicidal behaviour, which is known to affect suicidal behaviour in those exposed (the Werther effect). Interestingly, over 90% of prison cells in Ireland have in-cell television, and, while it is difficult to obtain official figures, it appears that the proportion of cells with in-cell television is substantially lower in England and Wales.

As Shaw et al (2004) demonstrate, prison populations often comprise individuals with multiple risk factors for suicide. We suggest that repeated exposure to vivid, detailed accounts of the methods apparently used in high-profile, apparently self-inflicted deaths in prison may be a critical additional risk factor in this population. We renew calls for responsible reporting of suicidal behaviour and for development of improved prison mental health services.


**Bresnihan, V. (2003) To be or Not to be, in Observations Cells? Dublin: Irish Penal Reform Trust.**

Ethnicity and suicidality

Gunnell et al’s (2004) interesting study came with useful learning points. However, while known as important factors that influence development and amelioration of suicidal thoughts, ethnicity and religion were not included in the study. As the world has become a small, or big, village, and as we live in a multi-ethnic and multi-religious society, I feel this should be considered as an additional limitation to the study. The relationship between religion and suicide became famous through Durkheim’s study in the 19th century.

In European countries, evidence suggests that the prevalence of suicide continues to vary in accordance with international differences in traditions, customs and religious practices (Cavanagh & Masterton, 1998). Cavanagh & Masterton suggested that the strength of these differences is decreasing because of homogenisation among countries. In my opinion, it is unlikely that this influence will completely disappear. In a modern secularised society, religion is still a meaningful and protective factor for many individuals in a suicidal crisis (Lonnqvist, 2000).

Makinen & Wassermann (2001) believe that much of the difference in suicidal behaviour between national groups can be connected with differences in cultural outlook, and state that ‘traditionally religion has been considered to be the matrix of culture’.

Various factors that influence development and amelioration of suicidal thoughts do not function separately. I wonder, had ethnicity and religion been included, how would this have affected the outcome?


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Attention deficit disorder in adults

The editorial on attention-deficit hyperactivity disorder and life-span development (Mc Ardle, 2004) is timely. However, it highlights the issues from the perspective of clinicians who may be directly involved in treating the disorder.

In general adult psychiatry, however, it is not widely recognised that (adult) attention-deficit disorder (ADD) is not uncommon and that people presenting with diagnoses of psychiatric disorders, mood disorders, anxiety disorders, etc., may also be suffering from unrecognised ADD. This has profound implications for both treatment and outcome. For example, if a person develops a hypomanic or manic episode superimposed on ADD, it is possible that the clinician unaware of ADD may end up treating the mood episode, as the baseline ADD may mislead the clinician into believing that the talkativeness and hyperactivity (of ADD) are an indication of elevated mood. The consequences include higher than necessary doses of medications, combination pharmacotherapy and increased length of stay in hospital. In patients with schizophrenia it is possible that the impairments in functioning caused by independent ADD may potentiate the poor functioning caused by schizophrenia. Again, if ADD is not recognised, it is possible that the poor outcome may be attributed to ‘resistant’ or ‘residual’ schizophrenia or perhaps to poor motivation. It is important to assess comorbidity such as ADD at the very first contact with mental health services, and early intervention service providers are ideally placed for this.

Regarding treatment, new strategies (other than stimulant medications) need to be developed, as stimulants may have destabilising effects on the baseline mental illness.


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Authors’ reply: We agree with Dr El-Adl’s comment that both ethnicity and religion may influence the incidence of, and recovery from, suicidal thoughts. Data on ethnicity were collected in the Office for National Statistics Survey that formed the basis of our paper (Singleton et al, 2001). Because of the relatively small sample size, only 122 (5.1%) of the individuals who reported ethnicity were from a Black or minority ethnic group and only seven of these experienced incident suicidal thoughts. Thus, specific investigation of the impact of belonging to a particular ethnic group was not possible. If the Black and minority groups are combined to give a single group, the odds ratio for incident suicidal thoughts in this group compared with the White group in analyses adjusted for age, gender and score on the Clinical Interview Schedule – Revised is 0.77 (95% CI 0.27–2.17). The breadth of the confidence interval indicates that the data are compatible with either a threefold reduction or a doubling in risk. Data on religion were not collected in the Office for National Statistics Survey of Psychiatric Morbidity.


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Risk reduction studies in schizophrenia

Niemi et al’s (2004) report does not truly address the implications of their findings. Their clinical implications (p. 16)
One hundred years ago

The care of the feeble-minded

The problem of the care of the feeble-minded may be said first to have received attention on anything approaching a general scale in Europe and America during the middle of the last century. In France the attempt to deal with this question may be traced to the beginning of that century and that country has been called the birthplace of the new education as it applies to the mentally defective class. Switzerland is summarise their results, but one fails to draw clinical sense of it or be in a position to use the information in clinical practice. One could be cynical about their findings; the offspring of mothers with schizophrenia or psychotic disorders are expected to be at increased risk, which could vary across studies owing to a multitude of factors, so the findings of the study are no surprise. The increased risk could be genetic, psychosocial or both.

The clinical implications of high-risk studies ought to help identify those at high risk and prevent health problems in them. A number of studies on risk reduction strategies have been reported for common medical problems, including diabetes (Ferdinand, 2004), cardiac disorders (Ferdinand, 2004) and atherosclerotic vascular disease (Heckam & Anand, 2003) and even complex multi-factorial disorders such as hypertension (Sheridan et al., 2003), to name a few. Although little can be done about the genetic component of the risk, the psychosocial and environmental effects can definitely be minimised. Multiple appropriate lifestyle alterations and stress protective strategies may be relevant. Furthermore, one expects that over time, the more recent studies should report relatively lower rates of elevated risk compared with those done decades earlier. Incidentally, Niemi et al. found an incidence of 6.7%, lower than the 16.2% found in a study reported in 1993, and 13.1% in one reported in 1995, showing a gradually decreasing receding trend. Niemi et al. attribute these differences to methodological factors, but one wonders whether the reduction can be attributed to preventive measures being implemented with those at high risk, inadvertently or inadventently.

What is the point of knowing that people are at increased risk of developing a disorder if nothing can be done with this knowledge?


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Author’s reply: Dr Chaturvedi questions the clinical relevance of knowing that offspring of mothers with schizophrenia are at increased risk of developing both psychotic and non-psychotic disorders, particularly because preventive measures are not available. However, preventive measures may be available in the future. Clinical high-risk studies already suggest that using specific preventive interventions, it is possible at least to delay the onset of psychosis in patients at incipient risk of psychosis (McGorry et al., 2002). However, the criteria for being clinically at high risk require that the individual is already showing psychotic-like symptoms or impaired functioning (McGorry et al., 2002). One of the goals in high-risk studies (including ours) is to identify early indicators of emerging psychotic disorders that could be detected before any impairment starts to develop.

Family interventions are rarely targeted at children of mothers with psychotic disorders, who often remain uninformed about their parent’s illness and have to cope alone with their parent’s symptoms and take additional responsibility for the family (Valiakalayi et al., 2004). We hope that the knowledge that the children are themselves at increased risk of developing mental disorders will enhance the planning and implementation of supportive measures and parental education for families where the parent(s) suffer from psychotic disorder. Such support should begin during pregnancy and continue through childhood and adolescence. These measures could also turn out to be preventive: the Finnish Adoption Study showed that the risk of developing schizophrenia-spectrum disorders among adoptees whose biological mothers had schizophrenia was much lower if they were raised in adoptive families with ‘healthy’ rearing patterns (Tienari et al., 2004).

Finally, Dr Chaturvedi suggests that there might be a genuine decline in the risk of developing schizophrenia among high-risk children. We discussed this possibility in our article, but the method of identifying the mothers in our study differs so much from those of the Copenhagen and New York high-risk studies that we still consider it premature to draw such a conclusion.


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another country which earlier than most occupied itself with the welfare of such defectives, being no doubt largely prompted thereto by the wretched condition of the cretins in its valleys. It is true that isolated efforts to collect the feeble-minded, together with the homeless and the outcast, for the purpose of care and supervision can be traced to much earlier dates but the general movement is associated with the period mentioned. In ancient times, it is well known that the congenitally weak-minded were either destroyed outright or allowed to perish, being deliberately exposed to the risk of death, unless, perchance, they were tolerated for the sake of diversion. The drastic methods of the ancients find a milder modern counterpart in suggestions for the asexualisation of the mentally defective, suggestions which have already in a limited way been put into practice in the United States. In the Middle Ages the feeble-minded appear often to have wandered unmolested, being regarded with a certain superstitious reverence (“les enfants du bon Dieu”), and doubtless some of the fools and the jesters of mediaeval times were recruited from this class. The village “fool” is still to be found, although there has of late years been a growing tendency to sweep all such feeble-minded persons into asylums for the insane, which is undoubtedly a mistaken course.

All schemes for dealing with the feeble-minded are necessarily based upon their classification and also upon the fact that cure does not take place but that even the best of them require a certain amount of supervision at the expiration of the period of training. For practical purposes these defectives may be classified as idiots and low-grade imbeciles, unimprovable or improvable in but slight degree, and mainly in self-help; imbeciles of higher grade, capable of being trained to such a degree as to be partially self-supporting; and the mentally feeble capable of training to the extent of being self-supporting. The needs of the first class are met by the Idiots Act of 1886, which permits the detention of idiots and imbeciles in special institutions. These, however, are far too few, large areas of the country being unprovided for. In default of special institutions these cases, as well as many of the trainable classes, are relegated to workhouses and asylums where they are totally out of place except, perhaps, in those rare instances in which it has been deemed worth while to make separate provision for them. Too often such children are found scattered about asylum wards where their presence is a source of irritation to the insane and is apt to give rise to degrading practices. It is desirable that it should be made incumbent on county councils to provide accommodation for this class which could be cared for on a simpler and cheaper scale than that required in the case of the insane. It is, however, when we come to considering the second and third classes, as defined above, of defectives that we recognise the inadequacy of the means at present available for their detention and training and the harm which in consequence results to society. Unfit for ordinary school education, turned adrift from home, these feeble-minded individuals wander about living as best they can. Their history is made up of vagabondage, larceny, incendiariism and criminal assaults. Feeble-minded young girls are received in a state of pregnancy into charitable institutions; feeble-minded youths are consigned to prison and transferred to the nearest asylum, where an anthropometric examination reveals abundant and pronounced stigmata of degeneration.

REFERENCE

Lancet, 11 February 1905, 370.

Researched by Henry Rollin, Emeritus Consultant Psychiatrist, Horton Hospital, Epsom, Surrey

Corrigenda

Impact of childhood abuse on the clinical course of bipolar disorder. *BJP*, 186, 121–125. In Table 1 (p. 122) the second column should be headed ‘No history of severe childhood abuse’ and the third column should be headed ‘History of severe childhood abuse’. The online version of this article has been corrected post-publication in deviation from print and in accordance with this correction.

Career choices for psychiatry: national surveys of graduates of 1974–2000 from UK medical schools. *BJP*, 186, 158–164. The third ‘Limitation’ (p.163) should read: Post-questionnaire surveys may not capture some of the subtleties of views about psychiatry and we did not ask those who did not choose psychiatry whether there are factors that might have influenced them to choose it.
The care of the feeble-minded
Henry Rollin
BJP 2005, 186:356-357.
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