Correspondence

EDITED BY KHALIDA ISMAIL

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Risks of combination neuroleptic treatment

I agree with Williams et al (2002) regarding the term ‘neuroleptic-resistant schizophrenia’ and the spirit of a ‘positive approach’ in managing it. The need for a biopsychosocial approach is also undisputed. However, the article appears to overemphasize the efficacy of psychotropic combinations and does not mention the associated risks. There is no advice to end the series of treatment trials at any point.

As the article points out, there is only one published randomised control trial (Shiloh et al, 1997) studying the efficacy of combining two neuroleptics. It is surprising that the authors did not measure the clozapine levels. There are other publications (e.g. Tyson et al, 1995) reporting a marked rise in clozapine level when another antipsychotic was added. The apparent benefit of combining sulpiride with clozapine may have been purely due to an increased serum level of clozapine. In other words, if adequate serum levels were achieved prior to the study, the combination may have produced no additional benefit at all. Other claims of efficacy of combinations based on clinical experience in only one or a few patients form a meagre evidence base.

There are clear risks associated with these combinations. The Psychotropic Drug Directory (Bazire & Benefield, 2001) warns about increased risk of agranulocytosis when other antipsychotics are combined with clozapine. There have been case reports (e.g. Godleski & Sernyak, 1996) suggesting such risk. Friedman et al (1997) reported ‘worrisome ECG changes’ when pimozide was combined with clozapine. Waddington et al (1998) reported that polypharmacy of antipsychotics was one of the predictors of reduced survival among people with schizophrenia.

As in the case of prescribing doses above British National Formulary recommended limits, there should be clear guidelines regarding the combination of two antipsychotics. This should include detailed discussion with the patient/carers regarding the indications and limitations of such treatment, physical investigations such as electrocardiography and a time-limited plan to review and to return to monotherapy if the combination is not producing any additional benefit.

Neuroleptics may not be able to provide complete remission of schizophrenia in every individual sufferer. Beyond a point the risks may outweigh the benefits, especially when used in combinations and in high doses. Accepting this is not therapeutic nihilism but realism.


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Antipsychotics, HERG and sudden death

The recent case-control study by Reilly et al (2002) showing an association between probable sudden unexplained death and current treatment with thioridazine in psychiatric in-patients underscores two fundamental issues essential for dealing with potential risks of this kind in the context of new, atypical antipsychotics. The first is that the abandonment of older drugs that have been used successfully such as thioridazine, even with the availability of newer compounds, can have profound consequences for some patients, as has been shown in the case of discontinuation of thioridazine in patients with learning disabilities (Davies et al, 2002). For those drugs that are being used successfully to control serious conditions, caution may be warranted in making changes that lead to the removal of drugs purely because of potential torsadogenic risks. Even those drugs that block the human ether-a-go-go-related gene (HERG)-encoded K+ channel, which is thought to mediate many of the cases of drug-induced long-QT syndrome, must be considered cautiously in this respect. Some pharmacovigilance estimates based on spontaneous reports of adverse reactions suggest that the risk of torsades de pointes for non-antiarrhythmic drugs, even those considered to be associated with risk, may be as low as 0.10 per million defined daily dosages, and that the consequent risk of sudden death may be as low as 0.025 per million (e.g. Lindquist & Edwards, 1997); even assuming a 1% reporting rate, this risk remains small.

The second issue is that given the fact that torsades de pointes is so rare, it has been proposed that this kind of arrhythmogenesis may be a ‘multi-hit’ phenomenon in which several risk factors must simultaneously be present (Keating & Sanguinetti, 2001). Furthermore, it has been suggested that in the normal ventricle, there is little risk of developing torsades de pointes because the normal functioning of the robust repolarising currents ensures a large repolarisation reserve, and it is by the occurrence of risk factors (e.g. female gender, hypokalaemia, bradycardia), which reduce the repolarisation reserve, that the likelihood of torsades de pointes is greatly increased (Rodent, 1998). For example, we and others have previously pointed out that low serum potassium attenuates HERG activity and that increasing serum potassium has been used to correct quinidine-induced acquired long-QT syndrome (Choy et al, 1997; Hancox & Witchel, 2000). Given that Reilly et al's
two control groups differed radically in their use of diuretics, and given that their model using control per case showed a significant odds ratio > 100 associated with the use of diuretics, it may be important to determine potential synergies for risk mediated by hypokalaemia directly, as well as including the use of diuretics in regression analyses.

As several of the new, atypical antipsychotics recently have been shown to block the HERG K+ channel, the clinical implications are that without a more complete understanding of the mechanism of risk, further studies examining this association for new atypical antipsychotic agents will require, where possible, prospective studies that can be used to determine the synergistic action of other known risk factors to be measured directly. Although mortality, even a low risk of mortality, is an unacceptable effect for a drug used to treat a non-fatal condition, the successful use of drugs such as thioridazine mitigates against the wholesale elimination of these drugs without due consideration for individual cases.


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### Decision-making and euthanasia

In a recent editorial Kelly & McLoughlin (2002) highlight the fact that the uncertain prognosis of most psychiatric diseases means that the objective accuracy of decisions on ‘physician-assisted suicide’ and euthanasia in this category of patients cannot be certified.

One important psychological issue, which parallels these views but applies to all cases of physician-assisted suicide and active euthanasia, is that decisions on these issues may be influenced by unintentional and even unconscious biases. One example of this phenomenon was presented in a recent study in which Swedish jurors were presented with a case description of a severely brain-damaged patient who was taken out of a respirator in the presence of muscle-relaxing drugs. The jurors were, most likely out of concern for the patient, generally supportive of euthanasia. However, since we varied the gender of the patient, as presented in the case description, we were also able to see that both male and female jurors tended to be most supportive of this kind of euthanasia when it was administered to a patient who belonged to the opposite gender (Sjoberg & Lindholm, 2003). Swedish jurors thus tended to be more impressed by the futility of the life of patients who were in important respects dissimilar to themselves.

Not only psychiatric, but almost all clinical decision-making is to a certain extent tentative and subject to the corrective forces of expectation and further empirical observations – but decisions that lead to the active and intentional termination of the life of a patient are not. We believe that this fact, which was also indirectly addressed by Kelly & McLoughlin, is important not only to the discussion of whether physician-assisted suicide should be administered to psychiatric patients but also to the discussion of whether physicians should engage in euthanasia and physician-assisted suicide and whether psychiatrists should take the risk of sanctioning such activities by assessing the mental status of potential subjects of such interventions.


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Retention in psychiatry
Seeking improved means of recruiting psychiatrists appears to be only part of the solution to the present shortfall of consultant psychiatrists. Another aspect of the problem, as mentioned in Storer’s editorial (2002), is the inability of psychiatry to retain trainees.

One potential factor contributing to the haemorrhage of trainees is lack of success at the membership examinations. Is it possible that this situation could be reappraised? It seems unfortunate that trainees who have already committed themselves to a career in psychiatry should have their prospects brought to an abrupt halt. Perhaps I am not alone in having had the experience of working with competent and enthusiastic people who found themselves in this predicament.

One hundred years ago

Crime in general paralysis
In the Journal of Mental Science for January Dr. W. C. Sullivan, deputy medical officer of H.M. Prison, Pentonville, has published an article on the medico-legally important subject of crime in general paralysis. While crime has been extensively investigated in recent years in association with conditions of arrested or distorted cerebral and physical development (criminal anthropology), less attention has been given to a class of criminals in whom the morbid aptitude for criminal acts is connected with acquired cerebral degeneration or defect, such as might be caused by alcoholic intemperance or general paralysis. The examination of conduct in chronic alcoholism shows a remarkable frequency of suicidal and homicidal impulse as well as a tendency to sexual crimes, a subject to which attention has already been called in these columns. In general paralysis, on the other hand, says Dr. Sullivan, the character of conduct was entirely different. A rough illustration of this might be given in statistical form. During nine years (1888 to 1896) among convicted prisoners certified as insane in the local prisons of England and Wales there were 274 cases (261 males and 13 females) in which the form of mental disease was considered to be general paralysis. Amongst these 261 male general paralytics homicide or homicidal attempts constituted the crime in nine cases, suicidal attempts were met with in eight cases, sexual offences in 13 cases, assaults in 21 cases, crimes of acquisitiveness in 144 cases, threats in eight cases, and other offences in 58 cases. Crimes of acquisitiveness were notoriously common in general paralysis, their most typical form being petty larceny, fraud, forgery, and embezzlement. Generally the circumstances and execution of the offence showed a characteristic silliness, though occasionally the general paralytic did commit robbery or fraud with an appearance of adequate motive and premeditation. The most important point to be noted was that this tendency existed in the exalted and optimistic variety of general paralysis and not in the depressed or melancholic form. Very often the impulses to theft or undue acquisitiveness preceded the grandiose delusions by a long period of time or were met with in the purely demented type of general paralysis without delusions. Besides this impulsive origin, paralytics who had lost money or blundered in their accounts might in a more lucid phase embezzle to make good the deficit – a point of practical importance in relation to the question of legal responsibility. Paralytics are also very amenable through their naiveté to criminal suggestion by others. Magnan quotes the case of a patient who was sent by his wife to steal in the Bon Marché, and Foville mentions two instances where paralytics were used as tools to utter forgeries. Acts of violence may be committed by paralytics when their grandiose tendencies are opposed, but the majority of grave acts of violence depend on a primary homicidal impulse generated by the more or less persistent state of emotional depression. Sexual offences in early paralysis – in the form of rape, defilement of children, and offences against public decency – are not uncommonly met with.

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More to social capital than Putnam
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Access the most recent version at DOI: 10.1192/bjp.182.2.172-a

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