Correspondence

EDITED BY KHALIDA ISMAIL

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 overemphasise 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 co-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 (Roden, 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

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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 militates 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 (Sjöberg & 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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More to social capital than Putnam

I would like to comment on the editorial by McKenzie *et al* (2002) regarding social capital and mental health.

Putnam's conceptualisation of social capital is the one that has caught the interest of policy-makers in recent years but it is pre-dated, by at least a decade, by Bourdieu's (1980, 1985) theory of capital which, I would argue, has more relevance for the study of social and health inequalities. Portes (1998, 2000) gives an accessible account of this dynamic view of social capital.

One of Bourdieu's main insights is that people consciously participate to build their various forms of capital and then *use* them to their advantage. In this way, social capital is a property of the individual, acquired though it may be through group membership. More importantly, social capital (along with all the other forms of capital) is then implicated in the production and reproduction of the very inequalities it is generally thought to mediate against. This dialectic poses some very real questions for the study of health inequalities over the life course, especially with regard to the possibility of disentangling any direct effects of social capital on health from the indirect effects of social capital through increased social mobility and access to economic capital.

This dynamic view of social capital also allows health research to go beyond examining health 'status' to investigate its role in the onset of and recovery from illness and poor health. Those with low stocks of capital are more likely to become ill and take longer to recover or are less likely to recover at all. Further, they are more likely to suffer adverse consequences of their illness in other fields, such as regaining employment, thus contributing to the widening of health inequalities.

Although I agree with most of the editorial on the potential of social capital as a heuristic device in studies of mental health, I was disappointed that it gave the impression of theoretical or conceptual consensus on the issue. I hope that my brief sketch will encourage researchers to go further than Putnam's ideas.

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