Correspondence

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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 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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