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Editorial

The Use of Higher-Dose Antipsychotic Medication

Comment on the Royal College of Psychiatrists' consensus statement

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The consensus statement provided by the Royal College panel (this issue, pp 448–458) is timely, well founded, and extremely useful.

Despite years of research and clinical experience, definite dose–response curves for antipsychotic drugs have not been well established. Shortly after the introduction of chlorpromazine, a large series of double-blind, placebo-controlled trials were conducted demonstrating its efficacy in the treatment of psychotic disorders. Klein & Davis (1969) reviewed 61 such studies and found that at daily doses of chlorpromazine above 400 mg, 27 out of 28 studies showed a clear superiority for chlorpromazine, whereas at doses below 400 mg/day, only 14 out of 33 studies found such a difference.

Subsequently, there has been considerable interest in exploring the upper ranges of tolerated doses to determine whether higher doses might produce a more rapid therapeutic response or a greater ultimate clinical improvement. In addition, clinicians have used high doses in an attempt to control violent or aggressive behaviour and as an alternative for patients who failed to respond adequately to more typical doses.

With patients not selected for refractoriness, those studies comparing high-dose (defined as greater than 2000 mg/day chlorpromazine equivalents) with standard-dose treatment found no significant advantage for the former (Wijsenbeck *et al*, 1974; Donlon *et al*, 1978, 1980; Ericksen *et al*, 1978; Neborsky *et al*, 1981; Rifkin *et al*, 1991). These results, though consistent across several studies, do not rule out the possibility that some patients may benefit from higher than usual doses, but better means of identifying them are sorely needed. (A drug blood level obtained in patients who fail to respond to standard doses could identify those patients who are either non-compliant or have unusually low blood levels.)

As Reardon *et al* (1989) have reported, there was (in the US) a substantial increase in the use of high dosages of high-potency neuroleptics during the late 1970s and 1980s, despite the lack of clinical research data supporting such use.

To some extent the wider use of higher doses of high-potency drugs resulted from the fact that many clinicians believe such doses are well tolerated. However, adverse effects such as akathisia (Barnes, 1992), which may be misdiagnosed and lead to non-compliance, are more frequently seen with higher doses (Levinson *et al*, 1990; Van Putten *et al*, 1990). In addition, it is hoped that the use of lower doses may help to reduce the risk of other adverse effects, particularly tardive dyskinesia, and it is often the case that the maintenance dose of neuroleptic is highly influenced by the acute dose.

In recent years, several random-assignment, fixed-dose studies have helped to clarify the risk : benefit ratio of different neuroleptic dosages (Levinson *et al*, 1990; Van Putten *et al*, 1990; Rifkin *et al*, 1991; Volavka *et al*, 1992).

The results of these studies strongly suggest that dosages above 15–20 mg/day of haloperidol or fluphenazine offer no advantage as a first line treatment for patients without an established history of neuroleptic refractoriness. It should also be emphasised that even with dosages in this range, akathisia and akinesia are serious clinical problems whose prevention and treatment should be a high priority.

As the consensus statement suggests, among patients judged to be refractory or poorly responsive, there is also no evidence that very high or 'megadose' treatment brings any more improvement than does continuing on a standard dose. We (Kinon *et al*, 1993) have reported preliminary results from a trial designed to compare frequently used alternative neuroleptic strategies on such patients. Forty-seven patients who failed to respond adequately (*a priori* response criteria required relative absence of psychotic symptoms) to an open four-week trial of fluphenazine 20 mg/day (plus benztropine 4 mg/day) were randomly assigned, double-blind, to one of the following: fluphenazine 80 mg/day; haloperidol 20 mg/day; or to continue on fluphenazine 20 mg/day. The double-blind phase lasted an additional four weeks. Only 9% subsequently responded, with no superior efficacy being associated with any of the three alternative treatments. These data would support the conclusion that significant increases in dose are not necessarily indicated even when patients do not respond adequately to standard doses. Christison *et al* (1991), after an extensive review of alternative treatments for non-responsive patients, concluded that clozapine, adjunctive lithium, and adjunctive benzodiazepines

have the best documented benefit (in that order), but that clozapine is the treatment which appears capable of producing the most dramatic improvement.

Although there may not be a clearly established relationship between high-dose treatment and sudden death, neuroleptic malignant syndrome or even tardive dyskinesia, Parkinsonian side-effects are dose related, and without evidence of clinical superiority it would seem difficult to justify the use of high doses, for this reason alone.

If higher doses are used, it is critical that the rationale be clearly documented, including response to previous treatment, target signs and symptoms, and plans for evaluating response. In my experience patients frequently receive high-dose neuroleptics (often with other medications) for long intervals without any clear documentation of therapeutic effect. Once such a regime is established, the treatment team may be reluctant to 'rock the boat' and reduce dosage, particularly if the patient has a history of violent or aggressive behaviour.

The consensus statement raises a very important and timely issue in its discussion of resources and their effect on treatment decisions. Adequacy of staff, physical facilities and staff training can have a major impact on the management of acutely psychotic patients. Response to limitations in resources or time pressure frequently contributes to higher than necessary doses. At the same time it is important to recognise the real hazards (including physical injury) and uncertainties involved in working with acutely psychotic patients in order to provide the necessary research data, clinical training and resources to establish optimum standards of care.

These problems may be compounded in many areas of the world by lack of alternative medications for acute agitation (e.g. lorazepam) or refractory patients (e.g. clozapine), lack of needles and syringes for intramuscular administration, and insufficient staff to evaluate and manage patients. Guidelines and consensus statements represent a goal to strive for whenever and wherever possible.

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