Conventional Antipsychotic Prescription in Unipolar Depression, II: Withdrawing Conventional Antipsychotics in Unipolar, Nonpsychotic Patients

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Background: In a Hull and Holderness Community NHS Trust audit of prescribing in unipolar depression, 55 patients were identified as taking a redundant conventional antipsychotic with no apparent diagnostic indication. Concerns regarding these patients' polypharmacy, duration of treatment, and risk of long-term or undetected side effects led to their being contacted with a view to the discontinuation of conventional antipsychotic treatment.

Method: All case notes were scrutinized to validate, as far as possible, the diagnosis of unipolar depression without psychotic features. Patients were invited for a review of their medication. Ratings of symptoms (Brief Psychiatric Rating Scale), depression (Hamilton Rating Scale for Depression), motor side effects (Abnormal Involuntary Movement Scale), and personal function (Independent Living Skills Survey) were made before and after conventional antipsychotic discontinuation. The study was conducted Autumn 1999–Spring 2000.

Results: None of the 55 patients were deemed to present comorbid depression secondary to any other diagnosis. One patient could not be contacted; 14 patients, who tended to be older, refused the review. Of the remaining 40 who were seen, 25 had already discontinued antipsychotic treatment; their chronicity of illness was half that of the 15 patients continuing antipsychotic treatment. However, only 11 of these 25 patients had their medications discontinued under consultant psychiatrist supervision following the audit; 14 patients had stopped medication of their own volition, or for unclear reasons. Of the remaining 15 patients, 13 had their conventional antipsychotic discontinued by us. There were clinically and statistically significant improvements in symptoms and side effects after antipsychotic treatment was discontinued, and a statistically significant improvement in personal health care function.

Conclusion: In this small sample, discontinuation of nonindicated conventional antipsychotic treatment was associated with clear benefits. Conventional antipsychotics should be used with caution in nonpsychotic depressed patients, particularly in the long term. Reluctance to discontinue medication in more chronic patients may be misplaced.

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Our audit of antipsychotic prescribing in unipolar depression[1] revealed 55 patients taking conventional antipsychotics with no apparent diagnostic indication. Even though their doses were small, the patients' polypharmacy, duration of treatment, and risk of long-term or undetected side effects prompted us to follow up the audit with an intervention. The intervention was designed to remove, if possible, redundant conventional antipsychotics from the medication regimens of these patients. We wished to examine the patients for differences in symptoms, side effects, and personal function before and after stopping conventional antipsychotic treatment.

METHOD

On completion of the audit,[1] all consultant psychiatrists were informed of the identities of their patients who were taking conventional antipsychotics with no apparent indication. Between 12 and 18 months following the audit, patients were approached by one of us (M.M.) and offered the opportunity to participate in a review of their medication in a research context. The local Health Authority Ethics Committee approved the study. Patients refusing to be seen were asked for permission to access their case notes, so that any bias could be estimated. The study was conducted between Autumn 1999 and Spring 2000.

Consenting patients were seen by M.M. in a research clinic supervised by A.M.M. All previous case notes were carefully scrutinized by M.M. in order to validate the

clinical diagnosis of unipolar depression without psychotic features ascertained at audit (J.A.W.V./P.J.T.).[1] In addition, M.M. looked for evidence of alternative diagnoses that could produce comorbid depression (substance abuse, neuropsychiatric disorder, schizophrenia, personality disorder) and clarified any such issues at interview. Final diagnosis was agreed on between M.M. and A.M.M. using clinical judgment during supervision.

M.M. administered to patients a symptom rating scale, the Brief Psychiatric Rating Scale (BPRS)[2]; a depression rating scale, the Hamilton Rating Scale for Depression (HAM-D)[3]; and a conventional antipsychotic motor side effect rating scale, the Abnormal Involuntary Movement Scale (AIMS), which includes items for parkinsonism.[4,5] Patients completed a self-rating instrument evaluating everyday aspects of personal function, the Independent Living Skills Survey (ILSS).[6] ILSS subsections rate adequacy in feeding oneself, grooming, doing housework, looking after one's health, managing money, using transportation, leisure activities, and employment.

Demographic and clinical data were noted, and the history of depression was described and discussed with the patient. A regimen of reducing and discontinuing the conventional antipsychotic medication was then agreed upon. A follow-up appointment was arranged 3 months later, at which time all patients were supposed to have stopped taking their conventional antipsychotic medications. At this point, the rating scales were readministered (end of study).

RESULTS

Of the 55 patients identified as taking conventional antipsychotics, 54 were contacted; 1 patient could not be contacted. Of the 54 patients, 14 (26%) declined to participate and were unwilling to allow access to their case notes. Only sex and age (available from the original audit data) were recorded for those patients declining review.

There were significantly more women (N = 36) than men (N = 18) in the sample of patients contacted (N = 54) ($\chi^2 = 6.00$, df = 1, p = .014), and this pattern was maintained in the smaller sample of patients who agreed to a review of their treatment (men = 12, women = 28). The mean age in the original sample (N = 54) was 47 years (SD 12.24). Those declining to have their medication reviewed (N = 14) were significantly older (mean age = 54.93 years, SD 12.67) than those 40 patients who were reviewed (mean age = 44.53 years, SD 11.02) (t = 2.93, df = 52, p = .005). Patients had been treated for between 1 and 30 years, the mean chronicity being 9 years. Data on family history of depression were conclusive for 31 patients, of whom 17 (55%) did have a family history.

M.M. evaluated 40 patients. In no patient was the consultant psychiatrist's clinical diagnosis found to be invalid. Only 15 patients (37.5%) were still taking a conventional antipsychotic at time of first assessment. The remaining 25 patients had discontinued this medication; 11 under outpatient direction because they had improved (N = 7) or had unwanted effects (N = 4). Six had discontinued the conventional antipsychotic on their own; for the rest (N = 8), no clear reason for discontinuation was ascertained. The group who had discontinued antipsychotic treatment did not differ significantly from those remaining on treatment regarding age, sex, or presence of a family history; however, there was a 2-fold difference in chronicity. Those continuing antipsychotic treatment had been ill for 14.6 years, as opposed to those who had stopped, who had been ill for 6.2 years. This difference was statistically significant (t = 3.3; 95% confidence interval = 3.2 to 13.6; p = .002).

Table 1. Changes in Outcome Measures From Baseline to End of Study (Mann-Whitney test) Among Patients Who Were Taking a Conventional Antipsychotic at Baseline (N = 15)

Scale	Baseline Mean	End Mean	Percent Change	p Value
AIMS	10.0	2.7	73% decline	.03
HAM-D	15.3	7.4	52% decline	.05
BPRS total	12.1	6.8	44% decline	.04
BPRS thought disorder	1.0	0.2	80% decline	.03
BPRS withdrawal/ retardation	2.7	1.4	48% decline	.02
BPRS anxiety/ depression	9.3	6.0	36% decline	.008
BPRS hostility/ suspiciousness	0.7	0.0	100% decline	.07
ILSS-health	24.7	27.0	88% to 96% rise[a]	.04

[a]Of maximum score.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, HAM-D = Hamilton Depression Rating Scale, BPRS = Brief Psychiatric Rating Scale, ILSS = Independent Living Skills Survey.

The mean daily dose of antipsychotic treatment, in terms of British National Formulary (BNF)[7] recommended maximum, was 25% (range, 7%–71%, SD 18%). Continuing patients at baseline were prescribed a mean of 2.3 psychotropic medications. The study measures were carried out with those patients who had already discontinued medication, and time since discontinuation was noted. Of those 15 patients still taking a conventional antipsychotic at time of first assessment, 13 had antipsychotic treatment discontinued by the review team. Of the 2 remaining patients, 1 was hospitalized after first assessment, and 1 declined to change medication. All were included in the analysis. Syndrome score changes were calculated for the BPRS regarding thought disorder, withdrawal/retardation, anxiety/depression, and hostility/suspiciousness.[8] Outcome variables at the end of the study were compared with baseline scores using the nonparametric Mann-Whitney test. Significant findings are detailed in Table 1; means are included for illustration.

All outcome measures, apart from ILSS subscales (excepting the health subscale), improved significantly. The other social function (ILSS) measures improved slightly,

but none significantly. A standardized composite of the ILSS subsection scores also failed to show significant improvement. Most patients performed at or near ceiling on most subsections. Regarding the BPRS subscales, patients scored much higher on the anxiety/depression subscale than the others, and the significance of the reduction in scores on anxiety/depression was much higher than that for the other subscales.

The group of patients already discontinued was compared with the group still taking a conventional antipsychotic at baseline. The results for the group of patients who had already discontinued were very similar to those of patients discontinued by ourselves at endpoint, in that the already discontinued group was significantly less symptomatic and had significantly fewer side effects than the baseline group ($p < .05$). Their health care function was also superior. Other aspects of personal function—feeding and use of leisure time—were significantly better than in the baseline group, with trends toward statistical superiority for doing housework, money management, and leisure activities. The group of patients already discontinued from conventional antipsychotic treatment was compared with the group discontinued by us at the end of study. There were no statistically significant differences on any variable. However, the AIMS mean for those already discontinued (mean = 0.7) was much lower than the AIMS mean at the end of the study (mean = 2.7). Nonparametric correlations were obtained on all outcome variables with respect to months since discontinuation for the whole group of 40 patients. No correlation was significant, although there was a trend for AIMS scores to reduce with increasing time off conventional antipsychotics ($r = –0.30$, $p = .07$). There was no correlation between motor side effects and percent BNF[7] maximum dosage.

DISCUSSION

Just over a quarter of patients contacted refused the intervention. Our finding that these patients were significantly older suggests that, possibly, older patients are more satisfied with their medications after longer experience of treatment, although chronicity data could not be collected on those declining participation. Alternatively or additionally, older patients may be less willing to try changes in their medication for fear of relapse.

Despite the fact that all consultant psychiatrists were informed of patients who were on a possibly redundant conventional antipsychotic at least 1 year before we contacted these patients, of the 40 patients we reviewed, only 11 had already had their conventional antipsychotic discontinued for sound clinical reasons under outpatient supervision. The 2-fold chronicity of patients not discontinued may reflect reluctance on the part of both psychiatrist and patient to "rock the boat"; however, this study did not demonstrate that discontinuation was associated with risk. On the contrary, conventional antipsychotic discontinuation was clearly beneficial in terms of symptoms and side effects. That we found the improvement in anxiety/depression on the BPRS to be relatively specific indicates that patient improvement may not be attributable to mere "ratings drift," despite our open methodology and a priori hypothesis.

Our results certainly do not replicate those of other studies that tried to discontinue adjunctive treatment in depression, in which half the patients relapsed[9,10]; however, most of the patients in those studies were either elderly, or their adjunct was a mood stabilizer rather than a conventional antipsychotic, or both. Nor are our results consistent with those earlier studies[11–14] that indicated increased efficacy of an antipsychotic/antidepressant combination over antidepressant monotherapy. However, there are some caveats regarding the present work,[1] and none of the studies looked at a unipolar sample without psychosis.

Conventional antipsychotic doses prescribed to these patients at baseline were not insubstantial, at 25% of maximum recommended dose on average. Because dose did not correlate with motor side effects, reducing but not stopping conventional antipsychotics could not be justified for patients as a group. Moreover, patients not discontinued at baseline averaged 2.3 psychotropic medications each. There would appear to be good reasons for trying to rationalize such regimens, including the risk of side effects, drug interactions, and compromising compliance.

The percentage reductions in symptoms and side effects observed in our study are large enough to constitute criteria for "response" in most clinical trials. However, the data were collected on an open basis, and numbers were small; the group discontinued from conventional antipsychotic treatment by us was not followed up beyond the end of the discontinuation period. Therefore, these results may be regarded as informing practice, but with the safeguard of longer follow-up for patients discontinuing conventional antipsychotic treatment. It is reassuring that the already discontinued group was very similar to or even functioning better than the group discontinued by us, particularly regarding baseline assessment findings; the side effects in those already discontinued had almost completely resolved. However, the sustained improvement in those discontinued from conventional antipsychotic treatment for a longer duration could be accounted for by other factors such as chronicity, which distinguished those already discontinued from those still taking conventional antipsychotics at baseline.

The function rating scale used in this study was performed at ceiling by most patients, which suggests that there was little room for improvement; it may be that a quality of life scale would be more revealing in this regard. Despite this caveat, health care function did im-

prove, statistically if not clinically significantly. Possibly the opportunity for a discussion and participation in one's own treatment was as important as stopping the conventional antipsychotic.

An obvious question regards the mechanism of improvement of depression and general psychopathology in these patients. Overall, these effects seem most likely to be owing to a relative enhancement of dopaminergic function, when receptors are no longer bound to conventional antipsychotic drugs. In other words, the mechanism is the same as that for the relief of motor side effects. This has been shown to be the case in schizophrenia, in that dopamine-2 receptor occupancy and depressive symptoms are highly correlated.[15] Indeed, augmentation of antidepressants with dopaminergic drugs is a recognized treatment strategy.[16] Both pergolide[17,18] and amantadine[19] may have some value, although 1 small controlled study of pergolide was negative,[20] as opposed to the positive study, which was open.[18] Pramipexole appears the most promising dopamine agonist to date, whether added to antidepressant treatment[21,22] or used as monotherapy.[23]

A final point from these data regards the effectiveness of audit processes for changing practice. Audit is necessarily cumbersome in the absence of clinically useful patient information systems and diagnostic precision on the part of consultant physicians. We did not have enough resources to hand search the more than 500 sets of case notes, as in our previous study,[1] so we do not know if new patients continue to be prescribed redundant conventional antipsychotics. We only know how many patients had been discontinued, with a little information about how they differed from those remaining on conventional antipsychotic treatment. The low rate of consultant physician discontinuation, just over a quarter at least a year later, suggests that dissemination of audit results, even with regard to specific patients, has less impact than would be ideal.

Concerns about the effectiveness of clinical audit have been expressed repeatedly[24]; it may be poorly planned and developed, and not integrated with related Trust activities such as research and development and risk management. Other barriers to effectiveness include lack of resources, lack of expertise in implementation, and interpersonal conflict.[25] Audit may be perceived as diminishing clinical ownership, facilitating litigation, reinforcing hierarchies, and isolating professionals.

Good audit requires modern medical record systems, effective training, dedicated staff, protected time, structured programs, and a shared dialogue between health care purchasers and health care providers. Such an environment should improve communications among professional groups, improve patient care, increase professional satisfaction, and improve the administration of services. Even assuming this counsel of perfection, however, audit should not be used in isolation to enhance professional behavior; its effects appear small to moderate, although potentially worthwhile particularly in prescribing practice.[26,27] Educational outreach visits appear to be a promising intervention, which may be combined with audit, once again focusing on prescribing behavior.[28]

It may be that the most effective way to resolve issues generated by audits like the one presented in this study is to implement a special intervention for patients identified as suboptimally managed. Consultants could be asked to review "refusers" of the special intervention within their ordinary clinical practice, in liaison with the intervention team. There would be no formal rating scales or other procedures that could be construed as research requiring consent; this would have the advantage of increasing numbers of patients intervened with, but in the absence of specific evaluation of outcome. Such processes, especially if implemented alongside appropriate continuing professional development, may well render audit exercises of real value in improving patient care.

Clinical Implications

Clinical implications of this study include the following:

- Stopping redundant conventional antipsychotics in depressed patients is associated with reductions in symptoms and side effects.
- Audit is enhanced by intervention to target suboptimally managed patients.
- Reluctance to change medication in more chronic patients may be misplaced.

This article is the second of a 2-part series. The first part appeared in our May 2003 issue.

Drug names: amantadine (Symmetrel and others), pergolide (Permax and others), pramipexole (Mirapex).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, amantadine, pergolide, and pramipexole are not approved by the U.S. Food and Drug Administration for the treatment of depression.

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