Factors important to psychiatrists when prescribing depot antipsychotics

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The relative benefits and disadvantages of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) has been an area of much interest since SGAs were introduced amidst high expectations of superior efficacy and improved side-effect profiles. In this article, Dr Kenicer et al. analyse a survey of psychiatrists to establish trends in prescribing preferences and the factors influencing them when prescribing antipsychotics. A key finding highlighted the need for an evidence based algorithm when prescribing these antipsychotics.
benefits of choosing SGAs over FGAs. The CATIE study\(^5\) was conducted to examine differences in efficacy and side-effect profile between oral perphenazine (FGA) and the oral SGAs olanzapine, risperidone, quetiapine and ziprasidone. Results indicated that no clear difference in efficacy could be established between the antipsychotics used in the study, and that extrapyramidal side-effects (EPSE) were also similar. The exception was for olanzapine, which was identified as having reduced rates of discontinuation while also being recorded as having the most side-effects overall.\(^5,6\) Similarly, the CUTLASS I trial\(^7\) did not find evidence that oral SGAs were superior to oral FGAs with respect to quality-of-life measures at one-year follow up, nor did it establish any significant difference in EPSE. In 2009 a systematic review of evidence comparing FGA oral antipsychotics and FGA LAIs by Haddad \textit{et al.} proved inconclusive, with contradictory evidence found during review.\(^8\) Adams \textit{et al.} in a 2001 meta-analysis of RCTs showed no difference in relapse or tolerability between oral and LAI FGAs.\(^8,9\)

Very few direct comparisons of first- and second-generation LAIs exist. Those that have been published continue to suggest that the differences are less clear than those proposed when SGAs were brought to market. Nielsen \textit{et al.} compared risperidone LAI with a range of first-generation LAIs, but found no evidence of superiority of risperidone LAI on a range of outcome measures.\(^10\) Similarly, Shajahan \textit{et al.} in 2010 identified that zuclopenthixol LAI treatment was less likely to be discontinued than risperidone LAI or flupentixol LAI, and that side-effects did not differ significantly between the three LAIs.\(^11\)

NICE guidelines for schizophrenia indicate that clinicians should apply the same considerations to choosing an LAI preparation as those for oral preparations.\(^1\) These include consideration of metabolic, extrapyramidal, cardiovascular and hormonal side-effects along with service user involvement in decision making where possible, adequate monitoring of physical health parameters and regular review of therapeutic response to target symptoms.\(^1\) If, as outlined above, many of the suggested differences between antipsychotic formulations are at present not clearly established by the available evidence, is this reflected in our prescribing practices? If not, what then influences our choice of antipsychotic for oral and LAI preparations?

Variability in prescribing habits of clinicians can be seen from the literature. Patel \textit{et al.} surveyed 102 consultant psychiatrists on their knowledge and attitudes to first- and second-generation antipsychotic LAIs,\(^12\) finding that LAI use in their area overall was decreasing but was equally distributed between FGAs and SGAs. Oral antipsychotic use, however, remained predominantly SGAs. Internal review of prescription frequencies by our local health board pharmacy team indicates that second-generation LAI prescribing is increasing in our area, suggesting possible regional trends within groups of clinicians in medication choice. Heres \textit{et al.} identified that more experienced prescribers showed increased likelihood of using LAI medication compared with less experienced prescribers.\(^13\)

Given that the literature remains varied in its scope and findings, the need exists for further robust research into the cost effectiveness of FGAs versus SGAs in both their oral and depot forms. As treatment options increase for service users and those prescribing for them, alongside ongoing pressures on prescribing budgets within health boards across the UK, the need for pragmatic and informed antipsychotic selection is clear. The relative scarcity of clinical evidence, particularly in the LAI patient group, however, means that this is a challenge. Our survey of 301 practising psychiatrists within Greater Glasgow & Clyde Health Board examines trends in prescribing choices and the factors that influence them. Results draw attention to areas where further education for both prescribers and their patients may be targeted to help promote collaborative decision making during treatment planning.

**Method**

A subgroup of the Greater Glasgow and Clyde Mental Health prescribing management group was set up to design, distribute and analyse data from an online survey examining a range of clinicians’ attitudes, knowledge and trends in use of antipsychotic medications. The survey comprised a range of questions in various formats examining clinicians’ grade, years of experience, perceived prescribing habits when using antipsychotics, and the reasons for these choices. Data were collected via a five-point rating scale response, free-text and prompted-choice selection. Free-text responses were coded by two raters and stratified into 12 main categories of response. Any discrepancies between raters were put to a third rater for confirmation. Prompted-choice categories were agreed in advance by the group as covering a broad range of the typical clinical factors that prescribers might take into account when selecting medication. The final version of the survey was hosted on a third-party hosting website. The target group of respondents were all practising psychiatrists of any grade in the Greater Glasgow & Clyde Health Board area. Respondents were invited to complete the survey by a centralised email request, with
a follow-up request after two weeks. The total number of respondents was 96, representing approximately 30% of psychiatrists invited to complete the survey. In total, 56 consultants, 14 core trainees, 15 higher trainees and 11 specialty grade/staff grade doctors responded.

Data were collated, coded and analysed for trends by the subgroup utilising Microsoft Excel and Access.

Results and discussion

i. Influence of clinical experience on selection of FGA LAI Vs SGA LAI

Responses to the question ‘Do you more regularly select first- or second-generation depot antipsychotics?’, (Figure 1) suggest that psychiatrists with more experience are more likely to prescribe from the full range of LAI antipsychotics. This may be due to them having accrued years of prescribing experience with both generations of antipsychotics leading to confidence and clinical preference in choosing between them. Conversely, less-experienced psychiatrists may have had relatively little exposure to FGA prescribing, which might explain their preference for SGAs.

The results outlined in Figure 1 describe LAI choice at any stage of a patient’s treatment. Clearly patients will often be treated with several different depot antipsychotics at different stages of their management due to lack of response, poor tolerability or patient preference. When asked specifically about their preferred choice of LAI for initiation of treatment (ie excluding subsequent choices at later stage of management) responses indicate an overall trend favouring second-generation LAIs, however, in this case, the percentage choosing SGA LAIs remained very similar for each cohort. As years of experience increased across the cohorts, the proportion of respondents reporting no preference appears to reduce as the proportion who chose FGA LAIs increased (see Figure 2). Again, this may reflect increasing confidence with clinical experience having used both generations of antipsychotic extensively, with preferred systematic approaches cultivated during a psychiatrist’s career. Furthermore, it is worth remembering that for more junior psychiatrists such as core trainees, the choice of LAI preparation will often not lie with the junior doctor themselves, instead being advised by a more senior clinician. The increased proportion of ‘no preference’ in the least experienced group may in fact reflect junior doctors seeking clarification before prescribing on behalf of senior clinicians within a given team.

ii. SGAs appear to have a lower perceived level of side-effects

Opinion on the relative side-effect profile of the LAIs was recorded from a number of questions and the results were generally consistently in favour of SGA LAIs. Respondents were invited to indicate any factors that influenced their reason for choosing either FGA or SGA antipsychotics at initiation of treatment. Fifteen per cent more clinicians selected side-effect profile and patient acceptability as key factors in selecting SGAs for their patients (see Table 1).

When asked to identify the single most important factor in choosing their preferred LAI at any stage of treatment, the perceived superiority of SGA LAIs was clearly accentuated (see Figure 3).

These findings were replicated when asked specifically about initiation of treatment with 74 per cent of respondents identifying side-effect profile and tolerability as being the main influencing factor in selecting an SGA LAI, versus only 26 per cent for FGA LAIs.

As indicated previously, there is very little evidence from direct comparative studies of FGA and SGA LAIs. Despite this, there seems
to exist an overall perception that SGAs are superior with respect to side-effect profile. Clearly ‘side-effects’ is a broad term that can encompass a wide range of different short, medium and long-term adverse effects of medication such as EPS, weight gain, metabolic syndrome, hyperprolactinaemia, sexual dysfunction and more. Our study asked only about side-effects in general rather than individual side-effects. However, it is interesting to note that SGAs appear to have an overall better perception despite an absence of comparative studies.

iii. Respondents did not indicate that marketing influenced their choice of medication

Only three respondents (one for FGAs; two for SGAs) indicated that marketing or the pharmaceutical industry may be a factor influencing their choice of antipsychotic. It appears that clinicians may underestimate the degree to which marketing, either present or historical, influence their current prescribing habits.

iv. Cost was not seen to be an influencing factor and was reflected in psychiatrists’ variable awareness of the cost of various drugs

Among the factors least commonly identified as influencing the decision to initiate FGA and SGA LAIs was their cost. At any stage of treatment, only those with a preference for FGAs indicated that cost was a factor in this preference, and of those, only 14 per cent indicated so. For initiation of treatment, 32 per cent identified it as an influencing factor for FGA LAIs and 27 per cent when initiating SGA LAIs.

The low values attributed to cost and cost-effectiveness could, in part, be a function of the generally poor ability to accurately identify the cost of various antipsychotic LAIs within broad cost ranges (see Table 2). Consultants fared the best in this exercise (see Table 3).

Interestingly, those who prescribe paliperidone LAI appear to have a greater understanding of its cost relative to those who do not. This perhaps indicates a more informed decision process when prescribing paliperidone, but may also reflect information sharing and education from pharmacy colleagues when more expensive preparations are selected. Clinicians also appear to underestimate the cost of Risperidone LAI, which may represent a perceived (false) correlation between duration of availability and cost (i.e medications which are no longer under licence and sold in generic form may generally be presumed to be cheaper).

v. Time for an algorithm?

It seems then that prescribing practice does not just stem from a straightforward appraisal of the current evidence, and that more complex variables, including prescriber demographics, experience using particular formulations, perceived (but not necessarily evidenced) characteristics of differing medications and regional factors, may all influence prescribing trends. Eighty four per cent of respondents indicated that a prescribing algorithm would be helpful as an aid to selecting antipsychotic LAI treatment for patients.

This perhaps reflects the challenges faced by clinicians in balancing the often competing

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**Table 2. Percentage of respondents accurately identifying the monthly cost of LAI medicines**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost / month</th>
<th>% Choosing actual cost range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flupentixol</td>
<td>£10</td>
<td>51%</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>£10</td>
<td>50%</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>£10</td>
<td>57%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>&gt;£150</td>
<td>36%</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>&gt;£150</td>
<td>55%</td>
</tr>
<tr>
<td>Risperidone</td>
<td>&gt;£150</td>
<td>18%</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>£10</td>
<td>42%</td>
</tr>
</tbody>
</table>
Original Research ❚ Antipsychotic prescribing

Table 3. Average proportion of each grade correctly identifying the correct LAI cost range

<table>
<thead>
<tr>
<th>Grade</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>CT1-3</td>
<td>29%</td>
</tr>
<tr>
<td>HST</td>
<td>36%</td>
</tr>
<tr>
<td>Specialty doctor or clinical officer</td>
<td>42%</td>
</tr>
<tr>
<td>Consultant</td>
<td>51%</td>
</tr>
</tbody>
</table>

can we handle the truth? Br J Psychiatry 2008;192:161–3.

Sir,

I assume their definition of ‘avoidance’ as ‘distressing memories, thoughts, feelings or memories of the event’ may be a post-production editing error. The avoidance referred to in the case is of poor engagement with services, relationships and other social functioning and alcohol misuse rather than behavioural avoidance of places or objects linked with the traumas. The authors might usefully additionally consider that propranolol is an effective anti-akathisia agent.

The case described has received trifluoperazine and risperidone over prolonged periods both which may have inadvertently contributed to his symptoms and if so the beta blocker would be expected to be rapidly effective.

A thought provoking paper.

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