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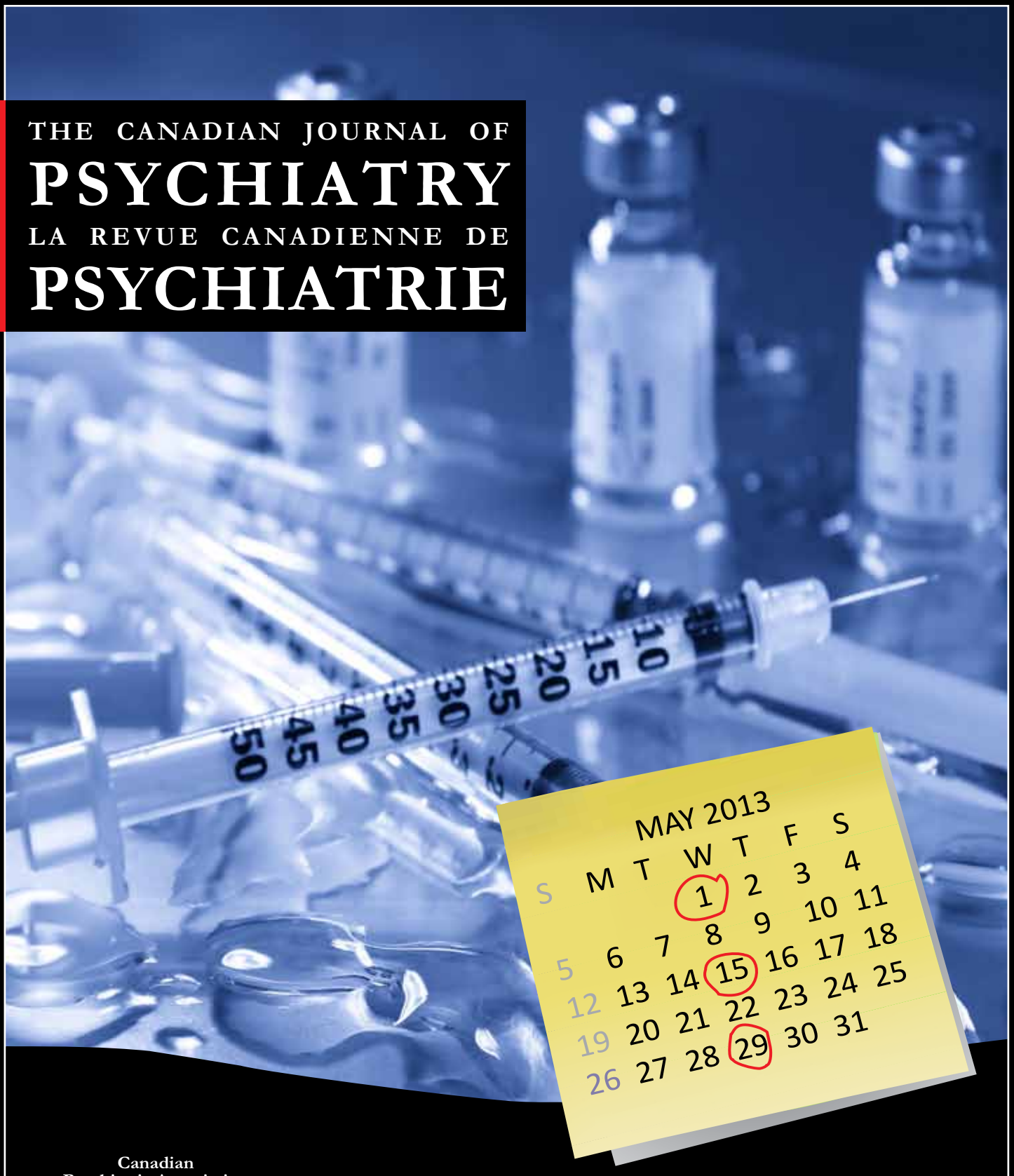

Canadian Psychiatric Association
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Long-Acting Injectable Antipsychotics: Recommendations for Clinicians

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Long-Acting Injectable Antipsychotics

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Guest Editorial

Why Are Canadians Complacent About Long-Acting Injectable Antipsychotic Therapies? Come on, Canada, You Can Do Better!

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As a psychiatrist specializing in serious mental illness, I am appalled by the shortcomings of the US mental health care system. On bad days, when dealing with disaster after disaster because of lack of continuity of care, I look north to Canada with envy. In Canada, you are able to treat schizophrenia in the context of an integrated psychiatric service system. When I received Dr Ashok Malla's generous invitation to be the guest editor for this special issue on the state of long-acting treatments for schizophrenia in Canada, I accepted with enthusiasm. I assumed that the situation regarding the use of LAI therapies would have to be better in Canada than it is in the United States because the LAI lends itself to integrated mental health services. Now I am not so sure. When reviewing the manuscripts, I was saddened to learn that many Canadian mental health services do not routinely use LAI therapies. Also, based on the focus group results in this issue, many Canadian psychiatrists seem to be biased against, or at least uncomfortable with, routinely using LAI therapies.

This supplement in *The Canadian Journal of Psychiatry* is a very important step toward reconciling variations in experience, enthusiasm, and proper understanding of LAI therapies within the context of psychiatric treatment services in Canada.

One of the frustrating aspects of reviewing LAI therapies is the tremendous variation among clinician attitudes about LAI therapy, and variation in the results of research studies on the relative usefulness of this approach. Having said that, I would suggest that there are 2 issues in particular that stand out. One issue is the disconnect between senior clinicians and younger clinicians. I have found that senior clinicians experienced in schizophrenia treatment tend to be strong advocates of LAI therapies, whereas younger clinicians who trained in the 1990s or later are generally less enthusiastic. I believe that these generational differences are partly explained by the relative benefit of LAI therapies over oral, which is not immediately apparent and often happens over years. Another explanation is secular changes in psychiatric training. Senior clinicians trained during a time when so-called depot therapy was commonly used, and observed the benefits over time; younger psychiatrists are less likely to have been trained in using LAI therapies, and may be less comfortable with how and when to use LAIs in community practice.

The second explanation for underuse is the apparent inconsistency found in the research literature on the relative benefits of LAI therapies. Cohort studies of real-world treatment environments tend to show better outcomes with LAI therapies than with oral, even though patient selection differences would be biased toward the opposite finding.[1] In contrast, most prospective RCTs of the oral, compared with the LAI, route do not tend to show such benefits.[2] The question becomes, Which kind of study design is most informative? While RCTs are usually viewed as the gold standard, in this instance, I count myself as believing that the epidemiologic studies have better face validity. My clinical experience has convinced me that LAI therapies, when properly integrated into a larger context of care, can change the course of an illness.[3,4] My frustration with the debate on the effectiveness of LAI therapies seems shared by some of the authors of this supplement, where many of the leading schizophrenia experts in Canada have developed sensible clinical recommendations for using LAI therapies, while also being aware of some of the limitations in the research literature and in clinical use.

This supplement helps guide Canadian clinicians and policy makers about individualizing decisions and recommendations for LAI therapy. General treatment guidelines invoke LAI medication as the magic elixir for the nonadherent patient. That is not good enough because such

treatment guidelines convey very little useful information about how LAI medication may be useful for the individual patient. We see an example of the fallout from oversimplified reliance on current guidelines in the transcript of one psychiatrist who equates LAI with noncompliance.

> *Facilitator: What type of patients would you consider an injectable for?*
>
> *Doctor: . . . mostly noncompliant . . .*
>
> *Facilitator: Noncompliant? [unspoken]*
>
> *Doctor: . . . it would be the noncompliants.*

Unfortunately, that does not get us very far. What does that mean? Does this mean patients will voluntarily accept a LAI medication after stopping oral medication? Unlikely! At the very least, as is done in this issue, recommendations need to differentiate the use of LAI therapy as an adherence tracking method from being a direct adherence intervention.

The clinical benefits of LAI therapy are much easier to recognize when there is a good understanding of exactly what is being expected by the recommendation of LAI therapy for the individual patient. For experienced clinicians who have followed schizophrenia patients during many years and have witnessed the differences in outcome associated with LAI therapies, the matching of patient profile with expectations arise from experience but do not find their way into the usual guideline. This special issue is a big step in helping less experienced readers to better understand expectations regarding LAI therapy for specific patient profiles.

Why have a supplement specific for Canadian psychiatrists? We think of pharmacologic treatments as somehow divorced from the logistic chain that makes a given medication available for our patients. Assuming equivalent financial coverage, with few exceptions, getting a prescription for an oral drug is going to be roughly the same, no matter where you are in the United States, Canada, or the United Kingdom. In contrast, the benefits—or last thereof—of LAI APs is much more sensitive to context. Even a so-called simple difference in number of days or hours in which a person can come in for an injection may translate into differences in outcomes.

Consider, in this supplement, the implications of what is said by the patient who seemed to prefer LAI therapy but said,

> I've had to skip a lot of classes to get my injection, and when I prioritize too my education is extremely important to me but not as important as my health, so I'm forced to choose [between classes and getting my medication].

Likewise, there is a great deal of variation in access to giving injections. In some parts of Canada, physicians may say, "I can't get anybody to give injection to my patients." My guess is no Canadian physician would say,

> I can't get anybody in the pharmacy to dispense my prescription for oral APs.

So, why have this special issue for Canadian psychiatrists? This consortium of Canadian experts have made a great contribution to helping explain national and regional practices across Canada, and offers a great deal of guidance for Canadian clinicians, educators, and policy makers.

Come on, Canadian colleagues, you can do better than this!

Warm regards from your neighbouring country,

Peter J Weiden, MD

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Information on funding and support appears on page 2S.

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Chapter 1

Long-Acting Injectable Antipsychotics: Evidence of Effectiveness and Use

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Key Words: depot, schizophrenia, long-acting injectable, second-generation antipsychotic, risperidone microspheres, paliperidone palmitate, first-episode psychosis, relapse, remission, adherence, hospitalization, community treatment order

Objective: To review the evidence for the role of long-acting injectable (LAI) antipsychotics (APs), especially the second-generation AP (SGA) LAIs, in the treatment of schizophrenia and to discuss the use rates of LAIs in Canada.

Method: A search of online medical databases was conducted of the published literature (1995–2012) of the effects of LAIs on the domains of remission, adherence, relapse, and hospitalization. Results obtained from randomized controlled trials (RCTs), systematic reviews, meta-analyses, and large-scale observational studies were included. Expert consensus data were also solicited on LAI use within a Canadian context.

Results: While the efficacy of LAIs, compared with placebo, is well established, the evidence from RCTs is equivocal for any specific advantage for SGA LAIs, compared with oral medications, probably owing to challenges in conducting such RCTs. Evidence from methodologically less rigorous studies and from clinical practice suggests some advantages in achieving and maintaining remission, risk of relapse, and hospitalization. The rate of LAI (first-generation AP and SGA) use from published outpatient studies is low at 6.3% in Canada, compared with 15% to 80% worldwide. However, there is a relatively high rate of use in specific early psychosis programs and in conjunction with community treatment orders in Canada.

Conclusions: LAIs are at least as effective as oral APs in the treatment of psychotic disorders. The former may have specific advantages for patients who demonstrate covert nonadherence. The underuse of LAIs in Canada needs to be better understood and addressed.

Antipsychotiques injectables à action prolongée : données probantes sur l'efficacité et l'utilisation

Objectif : Examiner les données probantes sur le rôle des antipsychotiques (AP) injectables à action prolongée (IAP), spécialement ceux de la deuxième génération (APDG) IAP, dans le traitement de la schizophrénie et discuter des taux d'utilisation des IAP au Canada.

Méthode : Une recherche des bases de données médicales a été menée dans la littérature publiée (1995–2012) sur les effets des IAP sur les domaines de la rémission, l'observance, la rechute, et l'hospitalisation. Les résultats obtenus des essais randomisés contrôlés (ERC), des revues systématiques, des méta-analyses, et des études d'observation à grande échelle ont été inclus. Les données de consensus des experts ont aussi été sollicitées en ce qui concerne l'utilisation des IAP dans un contexte canadien.

Résultats : Bien que l'efficacité des IAP, comparativement aux placebos, soit bien établie, les données probantes des ERC sont équivoques quant à un avantage spécifique des APDG IAP, comparativement aux médicaments oraux, ce qui est probablement attribuable aux difficultés de mener de tels ERC. Les données probantes d'études moins rigoureuses sur le plan méthodologique et de la pratique clinique suggèrent certains avantages pour atteindre et maintenir la rémission, le risque de rechute, et l'hospitalisation. Le taux d'utilisation des IAP (AP de première génération et APDG), tiré des études publiées sur les patients externes, est faible à 6,3 % au Canada, comparativement à 15 % à 80 % dans le monde. Cependant, le taux d'utilisation est relativement élevé dans des programmes spécifiques de psychose précoce et conjointement avec les ordonnances de traitement en milieu communautaire au Canada.

Conclusions : Les IAP sont au moins aussi efficaces que les AP par voie orale dans le traitement des troubles psychotiques. Les IAP peuvent présenter des avantages spécifiques pour les patients qui démontrent une non-observance secrète. La sous-utilisation des IAP au Canada doit être mieux comprise et traitée.

The efficacy of the FGA LAIs is well established.[1] In contrast, the SGA LAIs were introduced in Canada relatively recently. The implicit objective of using LAIs as a treatment option is to address the ubiquitous problem of nonadherence to APs.[2] With the introduction and widespread claims of superior effectiveness and improved adherence of the oral SGAs in the early 1990s, the use of the FGA LAIs declined markedly. However, the initial claims of superior effectiveness and improved adherence of oral SGAs have not been borne out in more recent controlled and randomized studies.[3] Continuing concerns about poor adherence to medication among patients and the recent availability of long-acting formulations of SGAs have sparked a renewed interest in the use of LAIs in the long-term treatment of psychotic disorders.

Here, we review the evidence for the effectiveness of LAIs in different domains and their use rates, with special reference to practice patterns in Canada. We confine ourselves primarily to the SGA LAIs and oral APs for comparison. The objective is to contribute toward a knowledge base and provide rationale for recommendations for their use along with additional evidence reported in this supplement.

Clinical Implications

- SGA LAIs are equally effective to oral formulations on multiple domains of outcome.
- LAIs may offer some advantage to patients with poor medication adherence in all phases of illness.
- LAIs are underused in Canada, suggesting a need for increased understanding of such underuse and corrective action.

Limitations

- The data on SGA LAIs are limited to only 2 currently available drugs (that is, RLAI and PLAI).
- RCTs are difficult to conduct with LAIs given the rigour of methodology; this may limit the types of patients recruited and such patients may not be representative of real-world patients.
- Outcome data with LAIs are highly influenced by the short-term nature of the studies and limited long-term data.

Methods

A literature search was conducted for the period from 1995 to 2012 using the following search engines: PubMed, PsycINFO, Web of Science, and Google Scholar. Search terms used in combination were "long-acting injectable," "risperidone," "antipsychotic," "depot medication" and "schizophrenia" or "psychosis" and "cost," "adverse effects," "hospitalization," "bias," "knowledge," "preference," "relapse," "remission," and "effectiveness." A separate search was also conducted with the terms "paliperidone palmitate" and "schizophrenia." Literature for inclusion was restricted to studies based on RCTs, high-quality observational studies, meta-analyses (not all primary citations were reviewed), as well as expert and systematic literature reviews (levels of evidence 1 and 2).[4] In addition, expert consensus data were also solicited on LAI use within a Canadian context.

LAIs in Canada

In addition to 5 FGA LAIs (that is, fluphenazine decanoate, fluphenazine enanthate, haloperidol decanoate, zuclopenthixol decanoate, and flupenthixol decanoate), 2 SGA LAIs are currently available in Canada (that is, RLAI and PLAI).

Efficacy

Level 1 Evidence: RCTs, and Systematic and Meta-Analytic Reviews

The efficacy of the first SGA LAI, RLAI, was evaluated in 3 pivotal trials, 2 short-term (12 and 24 weeks) studies, comparing RLAI with placebo and RLAI with oral risperidone, respectively, and 1 long-term (52 weeks) study involving a switch of stable patients to RLAI.[5–7] An early Cochrane review of RLAI analyzed data from 2 of the pivotal trials and reported that RLAI, compared with placebo, reduced psychosis (RR 0.5; 95% CI 0.33 to 0.83; NNT 9; 95% CI 7 to 26) and agitation (RR 0.6; 95% CI 0.39 to 0.92), but did not substantially influence hallucinations (RR 1.23; 95% CI 0.47 to 3.22).[8] Overall drop-out rates were high but greater for placebo than RLAI (RR 0.74; 95% CI 0.63 to 0.88; $z = 3.38$, $P < 0.001$). Compared with oral risperidone, there was no clear differences in global outcomes (RR 1.06; 95% CI 0.92 to 1.22) or mental state measures in stable patients with mild illness.

The efficacy of the second SGA LAI available in Canada, PLAI, was evaluated in 4 short-term (one 9-week and three 13-week) double-blind, randomized, placebo-controlled, fixed-dose trials.[9–12] A recently published Cochrane review found that, compared with placebo, PLAI-treated patients were significantly less likely to show no improvement in global state (RR 0.79; 95% CI 0.74 to 0.85; NNT 7; 95% CI 5 to 9), and less likely to experience a recurrence of psychosis, either in a specifically designed study (RR 0.28; 95% CI 0.17 to 0.48; NNT 5; 95% CI 4 to 6) or as an AE (RR 0.55; 95% CI 0.44 to 0.68; NNT 10; 95% CI 8 to 14).[13] Drop-out risk was lower with PLAI (RR 0.76; 95% CI 0.70 to 0.84; NNT 9; 95% CI 7 to 14) and there were fewer reports of agitation or aggression (RR 0.65; 95% CI 0.46 to 0.91; NNT 39; 95% CI 25 to 150).

A recent systematic review and meta-analysis of RCTs of both FGA and SGA LAIs of 12 months or more duration found that significantly fewer participants in the LAI group dropped out owing to inefficacy of treatment (LAIs 20.61%, orals 29.6%, $n = 1380$, RR 0.71; 95% CI 0.57 to 0.89, $P = 0.002$).[14] Conversely, a more recent meta-analysis of RCTs of LAI, compared with oral APs, reported no advantage of SGA LAIs, compared with oral SGAs, and concluded that studies in real-world patients were needed.[15]

Evidence from less rigorous open-label and observational studies suggests that patients transitioning from oral FGAs or SGAs to RLAI experience significant improvement in symptoms.[16] This effect was observed particularly in previously nonadherent patients.[17,18] Other similar studies of large samples[19–21] (range 1345 to 1876) show improvement on global measures, such as the Clinical Global Impression and the Global Assessment of Functioning. In addition, 2 open-label international studies with RLAI, have also reported a significant reduction in symptoms (PANSS) at 6 to 18 months.[22,23]

LAIs and Remission

Symptomatic remission in schizophrenia, operationally defined as achieving a low to mild symptom intensity level (≤3) on 8 core PANSS items sustained for 6 months,[24] has been shown to be a primary determinant of functional outcome.[25] There have been few studies of SGA LAIs specifically examining their impact on remission as per the new criteria. In a post hoc analysis of patients in a long-term study switched from oral FGA, oral SGA, or an FGA LAI to RLAI (25, 50, or 75 mg), 82 (20.8%) previously nonremitted patients achieved remission, and 156 of the 184 patients who met remission criteria at baseline remained in remission after 1 year of treatment.[7,18,26] Similar results have been reported from other studies of RLAI.[22,23,27–29]

LAIs and Adherence

The proportion of community patients with schizophrenia reported to be partially or totally nonadherent to oral APs ranges from 45% to 90%, with no differences evident between oral FGAs and oral SGAs.[30–33] A meta-analysis of 5 RCTs with 1141 patients and variable criteria for measuring adherence suggested no significant difference in adherence between those on LAIs (FGA and SGA), compared with oral (FGA and SGA) APs.[14] This is contrary to the belief held by many psychiatrists that LAIs are associated with better adherence than oral APs. This dichotomy likely exists because nonadherence is a deliberate act, thus a different formulation of medication is unlikely to influence it and that patients participating in RCTs are more likely to be willing to take treatment and to be cooperative, thereby obscuring any observable differences.

LAIs and Relapse

Adams et al[34] searched the Cochrane Database and extracted data from RCTs of LAIs. There was no significant difference in relapse rates between LAIs and oral APs. A meta-analysis of only RCTs ($n = 10$) of 1 year or longer, involving 1672 participants, indicated a significant superiority of LAIs, compared with oral medications, in reducing relapse rates, with relative and absolute risk reductions of 10% to 30% and 10%, respectively.[14] In a recent meta-analysis[15] of 21 RCTs with 5176 patients, pooled LAIs did not reduce relapse, compared with oral APs, in patients with schizophrenia. Analyzing individual LAIs, only the FGA fluphenazine LAI showed significant superiority, compared with oral APs, specifically at 24 months.

For the SGA LAIs, relapse rates investigated in a 2-year RCT with RLAI ($n = 329$), compared with quetiapine ($n = 337$), showed a lower rate (16.5%) and longer time to relapse in the former group, compared with the latter (31.3%).[35] The Kaplan-Meier estimate of time-to-relapse was significantly longer with RLAI ($P < 0.001$). In the only published RCT placebo-controlled study with PLAI, time-to-relapse favoured PLAI ($P < 0.001$, log-rank test) at both interim and final analysis ($n = 408$).[36]

Unfortunately, some patients with schizophrenia will relapse despite being adherent to medications, most likely owing

to the nature of the illness, stress, or concurrent substance abuse.[37–39] Although it may be anticipated that LAIs provide better adherence than oral APs and hence better relapse prevention, this is not always evident in RCTs. Therefore, one would consider that the evidence favouring LAIs is not unequivocal.

LAIs and Hospitalization

In the meta-analysis by Leucht et al,[14] based on 7 RCTs ($n = 1476$), and by Kishimoto et al[15] there were no significant differences between LAIs, compared with oral APs, on rehospitalizations. Only fluphenazine LAI was superior to oral APs.[15] However, an a priori planned sensitivity analysis using a fixed-effects model found LAIs significantly superior to oral medication on rehospitalization for any reason.[14] The effect was particularly significant if the oral and LAI were the same drug. On the contrary, a subsequent single-blind RCT, conducted with 369 veterans with schizophrenia or schizoaffective disorder, failed to reveal any significant differences on rates of rehospitalization (45% and 39%) and time to hospitalization (10.8 and 11.3 months), respectively, between the oral APs and RLAI.[40] A recent pharmacoeconomic review of 17 studies, of varying methodologies (RCTs, mirror image, and large-scale open-label), during 6 to 24 months, reported reductions in hospitalization associated with RLAI,[26] although numerous analyses from 1 long-term UK cohort did not show such reduction. In another non-RCT study (n = 1345), RLAI showed greater reductions in the number (reduction of 0.37 stays per patient, compared with 0.2, $P < 0.05$) and days (18.74, compared with 13.02, $P < 0.01$) of hospitalizations at 24 months than for oral AP patients ($n = 277$).[41]

Findings from a long-term, double-blind, randomized, multi-phase relapse prevention study (n = 213) indicated that treatment with PLAI from double-blind to end of OLE phase was associated with a significant decrease in the mean number of hospitalizations per person-year from 0.27 to 0.06 (78% reduction, $P = 0.05$) for patients treated with placebo in the double-blind phase, and an 88.6% reduction in hospitalization rates for patients (n = 381) from before enrolment to end of the OLE phase.[42]

In a prospective observational study of patients with schizophrenia, comparing RLAI (n = 40) with FGA LAI (n = 54), hospital discharge rates were 33 (83%) and 31 (58%) and readmission rates of 0% and 26%, respectively.[43] In another year-long study, 397 patients, switched from their previous oral AP to RLAI (modal dose of 25 or 50 mg), required significantly fewer (12%, $n = 48$, compared with 38%, n = 150) hospitalizations in the last 3 months of treatment 48 (12%).[6] Olivares et al[41] found that patients treated with RLAI (n = 1345) had significantly reduced rates of hospitalization, compared with those receiving oral APs (n = 277) along with a greater reduction in the mean number of days hospitalized in the RLAI, compared with oral risperidone group. Patients from 8 Canadian clinical sites who switched from their previous oral medication to RLAI (25, 50, or 75 mg) were significantly less likely to be hospitalized in the postswitch period (41.5 months), compared with an identical period (40.8 months) prior to use (50.7% and 4.3%, respectively). Duration of hospitalization also significantly decreased from 23.5 to 0.3 days per patient following the switch.[44]

Meta-analysis of RCTs show superiority only for fluphenazine LAI, compared with oral APs, and pooled LAIs show trend-level superiority, compared with oral APs. The findings of a nationwide cohort study of oral APs and depot APs after first hospitalization for schizophrenia carried out in Finland deserves mention.[45] Among 2588 patients, 1406 (54.3%) either did not collect an AP prescription within 30 days of hospital discharge or used their initial APs for less than 30 days. In a pairwise comparison between depot injections and their equivalent oral formulations, the risk of rehospitalization for patients receiving depot medications was about one-third of that for patients receiving oral medications. The authors emphasize that observational studies are the only way to investigate this issue as nonadherent patients cannot be forced to participate in RCTs.

HRQoL and Functioning With LAIs

The evidence of any differential impact on HRQoL from SGA LAIs and oral APs would, on the whole, be considered equivocal, despite some favourable results for LAIs from methodologically less rigorous studies. RCTs have generally failed to find any significant differences between groups using oral APs and RLAI on quality of life or on global functioning.[40] However, a post hoc analysis from a multicentre, placebo-controlled trial showed that 277 patients receiving RLAI (25, 50, or 75 mg) for 12 weeks showed significant improvements in 5 domains of the Short-Form Health Survey (that is, bodily pain, general health perceptions, social role functioning, emotional role functioning, and mental health), compared with the 92 placebo-treated patients.[28] In an observational study of a nonadherent patient population switched to RLAI, significant improvements on the Person and Social Performance Scale (60.0 to 69.1, $P < 0.001$) and the Drug Attitude Inventory Scale (from 2.78 to 5.07, $P = 0.006$)[17] were reported. It is unlikely that differences in HRQoL, not attributable to improvement in symptoms, can be detected between 2 treatments during a relatively short period of time and its clinical relevance remains unknown.

LAIs and AEs

Studies comparing RLAI with placebo suggest a low discontinuation rate owing to AEs (range 1.2% to 13%).[46] The most common AEs include headaches (range 7% to 28%), insomnia (range 7% to 28%), anxiety (range 7% to 24%), and psychosis (range 5% to 31%).[29] In a 12-month, multicentre, open-label switch study of nonadherent patients (n = 51), the most frequent AEs were insomnia (22.6%), increased prolactin (17.0%), and weight gain (13.2%).[17] In a short-term (12-week), double-blind, placebo-controlled study, patients randomized to receive RLAI gained a mean

Table 1 Use of LAI APs across the world

Study (year of publication)	Country or region	LAI use, %
Callaly and Trauer[59] (2000)	Australia	27.0
Fleischhacker et al[7] (2003)	Austria	50.0
Hanssens et al[60] (2006)	Belgium	21.5
Williams et al[61] (2006)	Canada	6.3
Sim et al[62] (2004)	East Asia	15.3
Xiang et al[63] (2006)	Hong Kong	37.0
Humberstone et al[64] (2004)	New Zealand	15.0
Dencker and Axelsson[65] (1996)	Sweden	50.0
Foster et al[66] (1996)	United Kingdom	29.0
West et al[67] (2008)	United Kingdom	36.0
Johnson[1] (2009)	United Kingdom	80.0
Paton et al[68] (2003)	United Kingdom	29.0
Valenstein et al[69] (2001)	United States	18.0
Covell et al[70] (2002)	United States	28.0
Shi et al[71] (2007)	United States	26.0

of 0.5, 1.2, and 1.9 kg in the 25, 50, and 75 mg groups, compared with a loss of 1.4 kg in the placebo group.[5] Data from other studies of RLAI of varying lengths suggest modest weight gain (mean 1.8 kg) with a dose of 25 mg and a low occurrence of dyslipidemia or hyperglycemia.[29,47] PLAI causes comparable weight gain and elevation in prolactin levels to RLAI.[10] AEs that were more frequently reported by patients receiving PLAI, compared with placebo groups, included insomnia, headache, dizziness, sedation, vomiting, schizophrenia, injection site pain, extremity pain, myalgia, and EPSs.[47–49] In RCTs, dose-dependent EPSs have been reported with RLAI, comparable to placebo, for the 25 mg dose (13% and 10%, respectively),[5] but higher than with oral SGAs.[28] There is a low annual risk of tardive dyskinesia with RLAI,[50] which is comparable to that of oral risperidone[51] and other oral SGAs,[52–54] while data from an observational study reported a decrease in baseline dyskinesia.[55] SGA LAIs, such as RLAI and PLAI, do not use an oil vehicle as their base and, with proper administration, there may be less risk of certain injection site complications.

LAIs and Early Phase of Psychotic Disorders

Relatively few studies have examined the effectiveness and clinical utility of LAIs in the early phase of psychotic disorders, despite very high rates of nonadherence during this phase and a high risk of relapse, mostly consequent on nonadherence to medication.[56] In a single-site, prospective, open-label study comparing RLAI and oral risperidone or haloperidol,[50] patients with FEP (36 completed full trial), following a medication wash-out period and an oral run-in period with risperidone, were switched to RLAI (25 to 50 mg).[57,58] Compared with patients treated with oral risperidone or haloperidol, RLAI-treated patients had significantly fewer all-cause discontinuations (26.0% and 70.2%, respectively, at 24 months, $P < 0.005$), greater reduction on PANSS total scores (–39.7 and –25.7, respectively; $P = 0.009$), higher rate of remission of positive symptoms (64.0% and 40.4%, respectively; $P = 0.03$), and lower relapse rate (9.3% and 42.1%, respectively; $P = 0.001$) among the responders.[58] Among patients who achieved remission of positive symptoms at some point during the study ($n = 32$; 64%), 97% ($n = 31$) remained in remission to completion. The relative paucity of long-term data in patients with FEP makes it difficult to determine the most appropriate use of LAIs in this population. The study by Tiihonen et al[45] (reported earlier in the LAIs and Hospitalization section) further supports using LAIs in early psychosis.

Use of LAIs in Canada

The frequency of the use of LAIs in predominantly outpatient samples of people with psychotic disorders from different countries (1996–2007) ranged from 6.3 to 80% (Table 1).[1,7,59–71] A Canadian study[61] reported that, across all patient types, only 6.3% were receiving LAIs, with rates varying across provinces: British Columbia (12.5%), Maritimes (7.6%), Prairies (6.6%), Alberta (5.7%), Ontario (3.1%), and Quebec (2%). We obtained Canadian data from IMS Health regarding the overall use of oral and LAI by province, which showed that use of LAIs nationally (FGA and SGA) in 2011 was 2.4% (Table 2). In a survey from England of 102 psychiatrists, 50% reported a decrease in LAI use during the previous 5 years, with 27% indicating no change and 24% reporting an increase.[1] Only a minority (4%) of psychiatrists rated LAIs (FGA or SGA) as a first choice

Table 2 Use of APs across Canada by type[a]

Province	SGA LAI %	FGA LAI %	Oral SGA %	Oral FGA %
Alberta	1.5	1.1	91.8	5.6
British Columbia	1.9	1.1	89.8	7.2
Manitoba	0.7	0.8	88.7	9.8
New Brunswick	1.8	1.0	89.6	7.6
Newfoundland and Labrador	0.5	2.5	85.6	11.3
Nova Scotia	1.5	1.6	84.3	12.6
Ontario	1.4	1.1	89.7	7.7
Prince Edward Island	2.0	0.0	81.7	16.3
Quebec	1.0	1.1	89.1	8.9
Saskatchewan	1.6	3.5	86.4	8.4
National	1.3	1.1	89.4	8.2

[a] These data were collected by IMS in the form of an independent study conducted by Janssen Inc, using IMS NPA Market Dynamics Moving Annual Total 2011, extracted May 2012 (Terri Lavery, 29 June 2012, personal communication). IMS is a major supplier of data and analysis to health care stakeholders. It uses a longitudinal database that tracks prescription purchases of Canadians, while preserving confidentiality and privacy.

preference for long-term maintenance of schizophrenia, and instead, most preferred to use oral SGAs. This would suggest that most psychiatrists today prefer to prescribe oral SGAs, despite the availability of SGA LAIs. Following a failure of oral SGAs to improve rates of nonadherence and hence rates of relapse and remission, the SGA LAIs may reignite an interest in the use of LAIs as a treatment modality, but little information is available regarding the frequency of use of SGA LAIs.

In Canada, LAI use also appears to vary according to the clinical setting and the stage of illness being treated. Specific inquiry into the clinical programs where the authors work was made about current LAI use and the proportion of patients receiving LAIs as part of a CTO. Almost all in the latter group had been placed on a CTO because of nonadherence to treatment and (or) a pattern of recurrent admissions to hospital; most of the patients were receiving LAIs as a condition of their CTO. In Halifax, Nova Scotia, in the Early Psychosis Clinic, a total of 17 of 270 active patients (6%) receive LAIs, including 3 who are on a CTO (100%). In the Assertive Community Treatment program in Edmonton, Alberta, there are 48 patients on a CTO, of whom 45 (97%) receive LAIs. In the PEPP in Montreal treating FEP, 24 (23%) of 112 patients are currently, or have been, on a LAI at some point, and of those receiving LAIs, 6 patients are also on CTOs (17%). In the Programme Troubles Psychotiques in Quebec, 15% of patients currently receive LAIs and 10% of patients are on CTOs, of whom 75% are on LAIs. In the PEPP in London, Ontario, 74 (23.4%) of 316 patients receive LAIs, with 77% on SGA LAIs, including 26 of the 31 (93%) patients on CTOs. In the early psychosis program in Victoria, British Columbia, 30 (14.3%) of 210 patients receive LAIs and 52 (65%) of 90 patients on a type of CTO are on a LAI. This is consistent with the literature, but raises the issue of LAIs being associated with coercion, and thus reinforcing the negative connotation of this modality of treatment.[72]

Conclusions

Improving outcome in schizophrenia and related psychotic disorders, while challenging, is a major goal of treatment. A relatively large proportion of variance in outcome is associated with potentially modifiable factors, of which nonadherence or partial adherence to treatment is one of the most common and difficult to address. Further, nonadherence is associated with lower rates of remission, higher rates of relapse, hospitalization, and (or) continued disability, as well as higher rates of medical morbidity and mortality from all causes. Achieving remission, and sustaining it for long periods, is critical for improving social and occupational functioning, especially in the early phase of the illness, when patients are more likely to show the greatest change in level of functioning, but, simultaneously, most likely to be nonadherent to medication.

The overall evidence discussed here, while not entirely convincing of the superiority of LAIs, compared with oral medications, especially if based on RCTs alone, is suggestive of equal effectiveness and some benefits of using LAIs in patients likely to be, and remaining, nonadherent, irrespective of the phase of the illness. In fact, while LAIs may not prevent nonadherence (because a patient can refuse the injection), their use does potentially allow for earlier recognition of nonadherence whenever a dose is missed,

and thus to be able to distinguish between non- or poor responsiveness from non- or partial adherence.

In contrast to RCTs, recent naturalistic studies support the advantages of LAIs, compared with oral APs.[73–75] These findings deserve merit as patients consenting to participate in RCTs of LAIs may not be representative of those prescribed LAIs in real-world settings.[76] In clinical practice, the uncooperative and nonadherent patients who are the most likely to get a benefit specific from the long-acting mode of administration are underrepresented in such studies. Further, the increased intensity of service generally provided during RCTs probably also contributes to increased adherence in patients treated with oral medication. Hence RCTs may underestimate the benefits from LAIs.[77] Given the costs incurred from hospitalization and care (79% of direct costs), compared with medication use (1% to 6%), the focus should be on using different medications that will increase adherence and eventually result in overall savings.[78] However, one cannot entirely overlook the costs associated with as SGA LAIs, compared with FGA LAIs, as barriers to prescribing. The ultimate decision should be based on a patient's preference, tolerability, AE experience, and the prescriber's comfort level. For patients who are clearly adherent to oral APs, there may be no reason or evidence to advocate a switch to LAIs. In any case, the relatively low use of LAIs in Canada needs to be better understood and addressed so as to make an effective treatment more readily available to a larger proportion of patients with psychotic disorders, especially when covert nonadherence is suspected.

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Chapter 2

A Qualitative Study of Experiences With and Perceptions Regarding Long-Acting Injectable Antipsychotics: Part I—Patient Perspectives

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Key Words: long-acting depot antipsychotics, antipsychotic long-acting injections, focus group, patient attitudes

Objective: Despite the well-acknowledged problem of poor adherence to antipsychotic (AP) medication, long-acting injectables (LAIs) that could improve adherence are underused in Canada. Attitudes concerning LAIs among patients and psychiatrists may contribute to this underuse. Our objective was to investigate perceptions of and attitudes toward LAIs among patients in Canada.

Method: Focus groups were conducted with 34 patients with a diagnosis of schizophrenia spectrum psychoses in 4 Canadian provinces. The focus groups inquired about experiences with and attitudes toward LAI APs. The sessions were audiotaped and transcribed verbatim, and transcripts were coded using a combination of deductive and inductive methods.

Results: Four themes emerged: awareness of and knowledge about LAIs; perceptions about LAIs; cost and convenience considerations; and issues arising from the coercive context under which LAIs were often prescribed. Nine patients had never heard about LAIs, and some others reported not having understood what was discussed with them regarding LAIs. Patients had typically heard about LAIs in either a context of coercion or of medication nonadherence. Patients had positive and negative perceptions concerning LAIs. The positive perceptions centred on relapse prevention and reduced effort in ensuring adherence, and the negative perceptions centred on financial costs and the inconvenience of appointments to receive injections.

Conclusion: To enhance LAI usage, some of the issues that need to be addressed are the inadequacy of information given to patients, the element of coercion involved in LAI introduction, the pragmatic barriers to LAI uptake by patients, and negative subjective perceptions about LAIs.

Une étude qualitative des expériences avec les antipsychotiques injectables à action prolongée et des perceptions à ce sujet : 1re partie — Perspectives des patients

Objectif : Malgré le problème largement reconnu de la mauvaise observance des antipsychotiques (AP), les injectables à action prolongée (IAP) qui pourraient améliorer l'observance sont sous-utilisés au Canada. Les attitudes à l'égard des IAP chez les patients et les psychiatres peuvent contribuer à cette sous-utilisation. Notre objectif était d'enquêter sur les perceptions et les attitudes des patients à l'égard des IAP au Canada.

Méthode : Des groupes de discussion ont été formés de 34 patients ayant reçu un diagnostic de psychose du spectre de la schizophrénie dans 4 provinces canadiennes. Les groupes de discussion portaient sur les expériences avec les AP IAP et les attitudes à leur égard. Les séances ont fait l'objet d'un enregistrement sonore et ont été transcrites textuellement, et ces transcriptions ont été codées à l'aide d'une combinaison de méthodes déductives et inductives.

Résultats : Quatre thèmes se sont dégagés : conscience et connaissance des IAP; perceptions des IAP; considérations concernant le coût et la commodité; et les questions liées au contexte coercitif dans lequel les IAP sont souvent prescrits. Neuf patients n'avaient jamais entendu parler des IAP, et d'autres ont déclaré ne pas avoir compris lorsqu'on a discuté avec eux des IAP. Les patients avaient habituellement entendu parler des IAP dans un contexte soit de coercition, soit de non-observance des médicaments. Les patients avaient des perceptions positives et négatives à l'égard des IAP. Les perceptions positives étaient axées sur la prévention de la rechute et l'effort réduit pour maintenir l'observance, et les perceptions négatives portaient sur les coûts financiers et la complication des rendez-vous pour recevoir les injections.

Conclusion : Afin d'accroître l'utilisation des IAP, il faut aborder certaines questions, notamment l'insuffisance de l'information donnée aux patients, l'élément de coercition présent dans l'instruction aux IAP, les obstacles pratiques à la prise d'IAP par les patients, et les perceptions subjectives négatives à l'égard des IAP.

Antipsychotics are essential for the effective management of schizophrenia and other psychoses, for treatment in the acute phase and for relapse prevention.[1] Medication nonadherence is highly prevalent (range, 10% to 88%) among patients with schizophrenia and related psychotic disorders, with median rates ranging from 41% to 55%.[1–3] This poor medication adherence is associated with significant personal, social, and economic costs. Specifically, poor adherence has been linked with higher levels of residual symptoms, higher risk and rate of relapse, increased hospitalization rates, lower rates of remission of positive symptoms, longer time to remission in the FEP, greater mortality and morbidity from multiple causes, poorer quality of life, and impaired social and independent functioning.[1,3–7]

Often seen as a dichotomous variable, adherence actually ranges between complete nonadherence (0%) and complete adherence (100%). Partial adherence can stem from factors such as lack of a daily routine, forgetfulness, ambivalence, and cognitive deficits,[1] and even relatively brief partial nonadherence (2 to 4 weeks) to oral APs has been associated with a significant risk of relapse among patients with recent-onset schizophrenia.[8]

In a recent reveiw, Barkhof et al[9] found no overwhelming evidence supporting any single intervention to improve medication adherence and attributed this, in part, to the heterogeneity of factors contributing to nonadherence.

Clinical Implications

- Improving perceptions about LAI APs and subsequently increasing their use may require that they be presented as one of the possible medication choices at every phase of the illness, including early in the course of treatment. More effective methods of imparting knowledge about LAI APs may be necessary to improve their use.
- To improve patient acceptance of LAIs, systemic changes may have to be implemented to reduce the inconvenience and costs involved with receiving LAIs.
- Patients do not necessarily have negative attitudes toward taking their APs in injection form.

Limitations

- A relatively small sample, from a limited range of treatment settings, was recruited, which may limit the generalizability of the results. However, an attempt was made to include younger and older, French- and English-speaking patients from early and later stages of psychoses, and from 4 provinces in Canada.
- Information regarding years since onset of illness was missing for focus group patient participants from 1 of the 4 sites.

Table 1 Patient demographic and clinical characteristics

Attribute	*n* (%)
Sex	
Male	27 (79.41)
Female	7 (20.59)
Education[a]	
<High school	9 (26.47)
High school	3 (8.82)
>High school	18 (52.94)
Ethnicity	
Caucasian	31 (91.18)
Asian	3 (8.82)
Age, years	
18–25	8 (23.53)
26–30	12 (35.29)
31–40	7 (20.59)
>40	7 (20.59)
Years since onset of illness[b]	
<2	4 (11.76)
2–5	7 (20.59)
6–10	5 (14.71)
>10	8 (23.53)

[a] Educational status is missing for 4 patients (11.76%).

[b] Years since onset of illness is unavailable for one site, London (*n* = 10; 29.41%).

Therefore, multiple strategies, including LAI APs, are needed to enhance medication adherence in psychosis.

Despite FGA LAIs having been found to reduce the need for hospital treatment among patients, compared with those receiving typical oral APs,[10,11] the introduction of SGAs that produced fewer neurological side effects led to a move away from prescribing depot typical medications to oral atypical medications.[12,13] Interestingly, the assumption that much nonadherence was associated with the neurological side effects of typical APs has not been supported by evidence.[1,2] The 2001 introduction of the SGA LAI, RLAIs, has rekindled interest in LAI APs.

There is considerable evidence suggesting significantly higher adherence rates with LAI APs, compared with oral APs.[10,14] By greatly simplifying medication regimens and allowing easier tracking of adherence, LAIs can be effective in tackling partial adherence, particularly when unintentional. Physicians, often underestimating nonadherence,[15–17] may also misidentify nonadherent or partially adherent patients as being nonresponsive to particular medications. Therefore, LAIs can be useful (albeit limitedly) in separating response and adherence issues. The evidence for effectiveness of SG LAIs, in particular, and their underuse in Canada have been reviewed in the first chapter of this supplement (see Chapter 1; Manchanda et al[18]).

Patients' and treatment providers' attitudes toward LAIs may influence both the psychiatrists' LAI prescribing habits and their acceptance among patients.[17,19–21]

A comprehensive literature review[22] has reported that 5 out of 6 reviewed studies found a patient preference for LAIs, compared with oral agents, in those receiving LAIs, while a more recent review[23] of a larger number of studies concluded that LAIs are often seen negatively by patients except for those already prescribed an LAI. To our knowledge, no study examining attitudes toward LAI APs has been conducted in Canada. Also, most studies have used surveys and (or) questionnaires, and only one study (to our knowledge)[24] has focused on subjective perceptions about and personal experiences with LAIs. From an open-ended interview study in Sweden, Svedberg et al[24] concluded that patients on depot treatment expressed favourable attitudes, based on painful memories of lost control during previous episodes. Therefore, our study sought to explore how patients with psychosis view LAI APs using focus group methodology.

Method

Focus group methodology was chosen for its potential to clarify diverse group norms and meanings[25] and to develop a complex, complete, and nuanced picture of the issue.[26,27] The discursive dynamics involved in focus groups can also yield a more complex and synergistic co-construction of meaning.[28,29]

Focus Group Participants

Focus groups were conducted in Halifax, Nova Scotia; Quebec City, Quebec; London, Ontario; and Victoria, British Columbia in 2010. The study was approved by the relevant ethics committees at each site. Coauthors (Dr Roy, Dr Tibbo, Dr Manchanda, and Dr Williams) helped in recruitment of patients by publicizing or discussing the study with relevant professionals and patients. Patients were selected if they had a diagnosis (Diagnostic and Statistical Manual of Mental Health, Fourth Edition) of a schizophrenia spectrum psychosis (clinical diagnosis provided by treating psychiatrist), were receiving outpatient treatment at the time of recruitment, and were considered stable enough to participate by the recruiting psychiatrist (Dr Roy, Dr Tibbo, Dr Manchanda, and Dr Williams). At each site, specific attempts were made to recruit younger and older patients; patients in early and later stages of psychosis; and patients who were or had been prescribed an LAI and those who had never been prescribed an LAI. Written informed consent was obtained and patients were compensated (Can$50) for reasonable out-of-pocket expenses (for example, transportation costs) and their time.

The final sample (clinical and demographic information in Table 1) included 34 patients—8 from Halifax, 7 from Quebec City, 10 from London, and 9 from Victoria.

Focus Group Sessions

A focus group interview with broad, open-ended questions regarding attitudes toward and experience with LAIs was developed. Patients also filled in worksheets to indicate whether they had ever been prescribed LAIs and to list advantages and disadvantages of LAIs. The patient focus groups lasted for 2 hours, on average. Interviews were conducted by 2 trained facilitators in French in Quebec and in English at the other sites.

Analysis

The focus group discussions were recorded and fully transcribed (and, in the case of the Quebec group, translated from French into English). The method of analysis[30] incorporated both the deductive approach outlined by Crabtree and Miller[31] and the inductive approach advocated by Boyatzis.[32] Following Boyatzis, coding involved recognizing important moments and encoding them, thus allowing the data to suggest themes and categories. The deductive approach involved the systematic analysis of transcribed data by the sorting of verbatim material into a template based on the specific questions for which they had been probed. The coding system was continuously revised during analysis. Two of the coauthors (Dr Iyer and Dr Malla) were involved in the coding of the transcripts. The final coding system and the allocation of blocks of text to particular themes were arrived at by discussion and consensus.

Focus groups, examining attitudes toward and prescribing patterns around LAIs, were also conducted with physicians at the same sites. The results from these are presented in an accompanying publication (see Part II; Chapter 3; Iyer et al[33]).

Results

All the analyzed data from the transcripts could be resolved into 4 main themes: knowledge about LAIs; perceptions about LAIs; cost and convenience considerations; and issues arising from the coercive context under which LAIs were often prescribed. Each category is described below, along with illustrative quotes. The patient-identified advantages and disadvantages of LAIs appear in Table 2, sorted by whether patients had prior LAI experience.

Awareness of and Knowledge About LAIs

Fourteen patients (41.17%) reported having taken an LAI at some point, while 9 (26.47%) reported currently being on an LAI. Nine patients (26.47%) had never heard about an LAI or had never had it discussed with them, stating, for example, "I dunno about the difference between the 2 [pills and injectables], but I'd really like to know."

Some patients reported not understanding what was discussed with them about LAIs or not having adequate information. One patient said, "It's been discussed, and I didn't really quite understand, so I didn't want to go there." Another said,

> I just heard about it when I was in the hospital. There's not enough information out there for people to . . . I didn't really understand what long-lasting meant, like how you could take it one day and it was spread over a long period or whatever . . .

Another patient said,

> I chose not to inject because of lack of information. I didn't have access to patient testimonials or really the side effects weren't explained very well to me as much as other medications. It just seemed a lot more scary at the time.

For most patient-participants, LAIs had not been introduced as an option at the beginning or even early in the course of treatment. One patient put it thus:

> Um, I would have liked to have been put on injectable drugs years earlier, cause otherwise I wouldn't had suffered more, I had another episode . . . I don't know if they would have been available earlier, but I would have preferred that because I would still be working these days.

Most patient participants reported that it was their psychiatrist who had initially discussed LAIs with them. Others had first heard about LAIs from their nurses, social workers, magazines and (or) pamphlets, and a roommate and (or) peer who had been prescribed an LAI. Two patients specifically mentioned the role of their parents in discussing and encouraging them to try LAIs. One said,

> Yeah, I think I lacked the awareness initially to understand the benefits that I could derive from taking it, but I think it [took] my parents . . . and their tearful, fearful eyes . . . for me to understand it, to say ok I'll take it, and I'll take it responsibly . . . and I eventually got better and I've done a little research on it and I'm happy to be on it.

Finally, one patient's awareness of LAIs came from participating in a research study that prescribed pills to one-half of a sample and LAIs to the rest.

Perceptions About LAIs

Several advantages or positive perceptions about LAIs emerged, particularly among patients who were currently on an LAI. Some quotes reflecting this are as follows:

> I'm sort of on my own path now, like I can take care of myself. I'm taking injectables, so it's like I don't even have to think about it anymore . . . gradually I've needed them [parents] less and less.

> I like [the LAI] because it has less side effects . . . I like it 'cause it's only once every 2 weeks.

> Well my medication is the injectable, and I prefer that, um, because I can't take my pills every day, I can focus on my recovery because I feel like I don't have to take the medication, it's always in my bloodstream in a constant, steady release . . . And

Table 2 Advantages and disadvantages of LAIs listed by people with and without prior LAI experience[a]

Perceived advantages	Perceived disadvantages
Previous experience with LAIs	
Nondrowsy pill; once every 2 weeks	Have not had any except [getting here in] rush hour traffic
No need to take medication every day	Beginning of injection; fatigue and agitation
—	More time required to produce effects after injection than with pills; stiffness; leucopenia; akathisia; hallucinations toward date of injection
Fewer side effects	Two-week cycles; more anxious at the end; frequent trips
Consistent dosage	Regular appointments
—	Inconvenient
Easier; sense of control over illness; case manager helps him remember; very little side effects; symptom reduction	Inconvenient to go to appointment [and not] miss work; cost; inconvenient hours
May help with weight gain and sedation	—
Less anxious; easier to take	Inconvenient; really dependent on it
—	Inconvenient hours
Do not need to remember to take medication	Very overpowering at first; not very effective as time passes and drug wears off
Steady release with equivalent quantity continually present in blood stream; not the ups and downs of the 24-hour formulation	Tied down to reporting to a clinic; difficult to leave town
Do not ever have to take pills every day; injectables let me be able to forget that I am on medication and lets me focus on my recovery; I do not have the option to not take my medication because it is always in my bloodstream	Have to go to the clinic every 2 weeks to get injection; when I want to travel somewhere, I have to make arrangements to take the medication with me and find a clinic to get injected at
No previous experience with LAIs	
—	Perception that it is mostly for noncompliant people, therefore like a punishment
Last long	Needles hurt
Safer to take	If you drink, it would not be effective
Easier to keep track of	Harder to travel
May help with weight gain and sedation	Cost; inconvenience
No need to remember taking pills	—
—	Loss of control over dosage
—	Not very effective; causes pacing and nervousness
For people who are forgetful about taking pills, the injectable makes remembering easy	—

[a] Advantages and disadvantages are recorded across the same line for each person.

> um yeah, it's convenient, yeah, I don't have to really worry about forgetting.
>
> I've tried both and I find the injectable to be much more advantageous for me, personally, rather than the pills, just because now I keep track of doing something twice a month, rather than perhaps twice a day or once a day, and there's also somebody else who's responsible for giving me the shot, so if I miss, you know it's not like I can forget and go off track, there's oversight again, and I'll have my case manager calling me up and saying you missed your appointment, you'd better get your butt down here and get your shot quick and I appreciate that, because it gives me an internal locus of control over the situation, rather than me being victimized by the unknown. I have a sense of control over my illness and it makes me—I'm proactive rather than reactive . . . I'm probably good for 2 weeks, so now I don't have to worry about it, I can forget about it, I can go about my life.

Interestingly, none of the patients on LAIs regarded them as being painful or found the pain or the needle to be dissuading. Conversely, 2 patients with no previous LAI experience mentioned the needle as a deterring factor, as follows:

> Um, well, I don't really have a phobia of needles but if I can avoid taking a needle, I will. Because it does hurt a little bit. A pinch. Yeah, I don't want to be a human pin cushion.
>
> I don't like needles at all, unless it's tattooing, I stay away from needles altogether, I just have a fear of that . . . in my family there's some addiction issues.

A few patients cited feelings of not being in control as the reason for which they had not taken or would not take an LAI. Below, 2 patients describe feeling more in charge with pills than they would with injectables:

> With the needle, I'm dependent on going to the appointments. I'm not sure if it's a real concern, but when I take my pills, it means that I can bring them with me, I can manage them on my own until I run out, right?
>
> It just worries me a little bit . . . like I feel like I had a little bit more control taking the pills. Like I can take it, I take clozapine, it just makes me really tired when I have my heavy dose. So I can, in the evening if I want to play a board game or whatever I can wait until after to take it.

One participant, who was in the unique position of having been on an LAI and currently being prescribed oral APs, contrasted the 2, stating,

> On the 2 occasions I was on them [LAIs], I did appreciate the fact that I only had to show up at the clinic infrequently and I liked the steady state effect, but uh with the oral medications, I like taking charge, I like taking them an hour sooner or an hour later depending on how I feel. I'm participating in my own wellness, [rather] than being put on a leash and having to report to hospital for the injectable.

Threat and External Control Issues

Eight out of 14 patients who were or had been on LAIs were initiated on LAIs either via a CTO (often after several episodes of nonadherence followed by a relapse and [or] hospitalization) or during an involuntary hospital admission. Specifically, 3 out of 14 patients (21.43%) were initiated on LAIs during an involuntary admission (2 of these were later put on a CTO) and 5 out of 14 patients (35.71%) were taking, or had taken, LAIs because of a treatment order. Some of them spoke about working through initial feelings of anger and disapproval toward the LAIs after perceiving their significant advantages. Here, a patient expresses gratitude that she "was persuaded" to go on LAIs, "Um, if I hadn't been persuaded, I probably would still be noncompliant, so I'm thankful I was persuaded." Others still retained negative feelings about having been coerced to take medications. One such patient said,

> The only time I was ever [on an] injectable . . . was when I was hospitalized, for the psychiatric assessment or whatever, then I get away from the hospital and I get away from psychiatrists and I dropped my meds all the time. My experience wasn't good, I didn't learn from anyone, it was just something that was forced on me. I didn't have a choice in the matter . . . and when there was a choice, I chose not to take it.

Such coercion may also prevent some patients from assenting to LAIs, as evinced by this quotation:

> Well, for me, when I was given the option, I kind of felt like someone [would be] looking over my shoulder with the injectable, like it wasn't my choice.

The initiation of LAIs among 6 out of 14 patients (42.86%) involved neither a CTO nor involuntary hospitalization. Even among these voluntary initiates, 2 had been presented with an ultimatum or a threat of being placed on a CTO if they refused LAIs ("It was a bit hard. I didn't have much choice. It was take this or we're going to court"). Others reported that it was brought up in the context of their nonadherence, "For me, it was because I stopped."

Other reasons for voluntarily choosing LAIs included persuasion or pressure by family and (or) treatment team ("took injections to get people off my back") and convenience ("I decided to start taking the shot just because you know it would help with taking it on time every single month, and, uh, it was just added to the convenience"). One patient felt that LAIs were an "intelligent" option.

Convenience and Cost Considerations

One of the 2 pragmatic obstacles to taking LAIs identified by the patients was the inconvenience of frequent (usually fortnightly) clinic appointments, often during the typical work or school day. The following quotes illustrate this point:

> You have the impression of losing all day.
>
> What I don't like about the long-acting injectables is you have to go and get them during clinical hours, like Monday through Friday, and for me, like, I would rather not tell an employer that I have to get an injection, and go in and get on a Saturday . . . or a Sunday, and that's not really an option.
>
> I've had to skip a lot of classes to get my injection, and when I prioritize, too, my education is extremely important to me but not as important as my health, so I'm forced to choose . . . it's not the most convenient time . . . in the 9 to 5 type of society that we live in. And it's just, there's an overlap there, I think it's not necessarily beneficial for the patient.

The financial costs of LAIs were often discussed as another obstacle, particularly at sites outside Quebec.

Consider the following quotes:

> The injectable is more expensive than the pills. It's like seven hundred dollars a month.
>
> It's not cheap . . . it's an undue burden upon them [referring to his parents who were covering the cost of his LAIs].

Pragmatic inconveniences were mentioned by a few patients as reasons for eschewing the LAI option. The following dialogue is exemplary:

> *Patient 1: I can't travel for longer than 2 weeks.*
>
> *Patient 2: Uh, I needed to come back here every 2 weeks for the injections so I miss work and everything, so I couldn't do much.*
>
> *Patient 3: The travelling would be a pain in the butt.*

Factors suggested by patients as conducive to increasing LAI uptake included LAI cost reduction; flexible clinic hours (for example, evening and weekend); the availability of time ranges instead of fixed times for LAI appointments; and the option of being injected at home ("Because if you calculated that 1 nurse travels for 15 patients, it means less travel than 15 patients who travel for 1 nurse"). The need for removing pragmatic barriers was summed up beautifully by one patient who said, "To facilitate access means to facilitate treatment."

Discussion

Our key findings under the 4 main themes were as follows:

1. *Knowledge*. A considerable proportion of patients with psychotic disorders may be totally unaware of the LAI option. Another large subgroup may have inaccurate or incomplete information. Patients with psychotic disorders are rarely presented all available choices (one of which is LAIs) when treatment is initiated. Discussion of all available options may lead to improved knowledge and greater adherence to any chosen treatment option.
2. *Perceptions*. Consistent with previous literature,[17,24] attitudes toward LAIs were generally favourable among people currently taking LAIs. While it is often assumed that patients disfavour LAIs because of a fear of needles,[21] we found that this did not hold true across the board. While we did not specifically probe about this fear, none of the patients currently on LAIs, and only 2 patients with no LAI experience, spoke about the needle or pain. Similarly, perceptions of being able to manage the illness on one's own are highly subjective. While some perceived greater control with pills (choosing when to take them), others perceived greater control over the illness with LAIs (reduced likelihood of relapse because of forgotten medication).
3. *Threat and External Control*. LAIs are generally introduced in a context of explicit (for example, court-ordered) or implicit (for example, threat of a court order) coercion. The introduction of LAIs at the treatment junctures wherein coercion comes into play may be an additional barrier to LAI acceptance among patients.
4. *Cost and Convenience*. Patients identified the frequency, timing, and high costs of LAI injections as significant disadvantages.

Our findings have important clinical and systemic implications. LAIs, along with all available treatment options, should be presented to all patients with psychosis, regardless of the stage of illness or treatment, in a respectful and easily comprehensible manner. This would be in keeping with the spirit of shared decision making and informed consent.[34–36] It would also be consistent with the emerging idea that LAIs may have clinical utility, even in the early stages of psychosis.[37–39] Presented early on, the LAI option would not be associated only with more difficult (for example, a relapse following suspected nonadherence) or coercive (for example, CTO being sought) junctures of treatment. This is also likely to improve patient perceptions and acceptance of LAIs. Clinicians may benefit more from exploring patients' subjective perceptions of LAIs rather than by basing treatment decisions on their own assumptions thereof. Our finding that some patients chose LAIs because they saw it as intelligent or convenient is consistent with the second cluster of patients for whom LAIs were appropriate according to Heres et al.[40] They described this cluster as having a "high level of insight, openness to drug treatment and profound knowledge about the disease" and contrasted it with the first cluster of patients with "episodes of non-compliance and relapses in the past."[40, p 1987]

Concerted efforts are needed to address potentially malleable pragmatic factors that impede LAI acceptance. For instance, clinics could offer weekend appointments, home visits, or ranges of time for administering injections. The cost of LAIs, currently borne out of pocket, is burdensome for most patients. Systemic and policy-level changes are needed to

address this issue because even minor changes in costs to patients are known to impact adherence.[41–43]

Our study has several limitations. We used a relatively small sample (4 groups) from a limited range of treatment settings and with relatively higher rates of prior experience with LAIs than is found in the general patient population. It is possible that patients who consented to participate were likelier to be medication-adherent and less likely to be on CTOs. The number of focus groups was decided prestudy; thus sample size was not determined by "point of saturation"[44, p 2] considerations. These sampling issues limit the generalizability of our findings. However, an attempt was made to include younger and older patients, patients from early and later illness stages, and patients from 4 Canadian provinces. Information regarding years since illness onset was missing for participants from one site. Specific probing on certain topics like the fear of needles and how the cost of LAIs is borne (for example, state insurance, private insurance, out of pocket, and family support) would have been beneficial. Despite these limitations, the use of focus group methodology yielded important insights that may have been missed with exclusively questionnaire and (or) survey methodology. These insights have implications for addressing the issue of underuse of LAIs, which, in turn, can help improve medication adherence in people with schizophrenia and other psychoses.

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Chapter 3

A Qualitative Study of Experiences With and Perceptions Regarding Long-Acting Injectable Antipsychotics: Part II—Physician Perspectives

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Key Words: depot antipsychotics, first-generation antipsychotics, second-generation antipsychotics, antipsychotic long-acting injections, focus group, physician attitudes

Objective: In many countries, including Canada, a small proportion of people with psychotic disorders receive long-acting injectable (LAI) antipsychotics (APs), despite their demonstrated effectiveness and possible advantages for improving adherence rates. Attitudes regarding LAIs among physicians may influence their prescribing practices and thereby contribute to the underuse of LAIs. Here, we report on a qualitative study of perceptions and attitudes toward LAIs among psychiatrists in Canada.

Method: Focus groups were conducted with 24 psychiatrists in 4 Canadian provinces. The focus groups inquired about experiences with and attitudes toward LAI APs. The sessions were audiotaped and transcribed verbatim, and transcripts were coded using a hybrid process of deductive and inductive methods. A brief pre-focus group questionnaire was administered.

Results: The pre-focus group questionnaires indicated that psychiatrists in our study prescribed the oral formulation of APs most of the time and had limited experience with LAIs. The focus groups yielded 4 main themes: limited knowledge about and experience with LAIs; attitudes toward LAIs (beliefs about negative perceptions of patients regarding LAIs, personal bias against needles, and consensus about some advantages of LAIs); prescribing practices around LAIs (generally seen as a last-resort option for patients with a history of nonadherence); and pragmatic barriers to using LAIs (for example, cost, storage, and staffing).

Conclusion: Several factors may be contributing to the underuse of LAIs and the continuing stigmatized and coercive image of LAIs. Psychiatrists may benefit from better education about LAIs, and from self-examination of their attitudes to LAIs and their prescribing practices.

Une étude qualitative des expériences avec les antipsychotiques injectables à action prolongée et des perceptions à ce sujet : 2e partie — Perspectives des médecins

Objectif : Dans de nombreux pays, dont le Canada, seule une petite proportion de personnes souffrant de troubles psychotiques reçoit des antipsychotiques (AP) injectables à action prolongée (IAP), malgré leur efficacité démontrée et leurs avantages possibles d'améliorer les taux d'observance. Les attitudes des médecins à l'égard des IAP peuvent influencer leurs pratiques de prescription et subséquemment contribuer à la sous-utilisation des IAP. Ici, nous faisons le compte rendu d'une étude qualitative des perceptions et des attitudes à l'égard des IAP chez les médecins du Canada.

Méthode : Des groupes de discussion ont été formés de 24 psychiatres dans 4 provinces canadiennes. Les groupes de discussion portaient sur les expériences avec les AP IAP et les attitudes à leur égard. Les séances ont fait l'objet d'un enregistrement sonore et ont été transcrites textuellement, et ces transcriptions ont été codées à l'aide d'une procédure hybride de méthodes déductives et inductives. Un questionnaire abrégé a été administré avant le groupe de discussion.

Résultats : Les questionnaires précédant le groupe de discussion ont indiqué que les psychiatres de notre étude prescrivaient la formule orale des AP la plupart du temps, et qu'ils avaient une expérience limitée des IAP. Les groupes de discussion ont dégagé 4 principaux thèmes : une expérience et des connaissances limitées des IAP; les attitudes à l'égard des IAP (croyances que les patients ont des perceptions négatives à l'égard des IAP, préjugés personnels contre les aiguilles, et consensus à propos de certains avantages des IAP); les pratiques de prescription des IAP (généralement vus comme une option de derniers recours pour les patients ayant des antécédents de non-observance); et les obstacles pratiques (par exemple, coût, entreposage, et dotation en personnel) à l'utilisation des IAP.

Conclusion : Plusieurs facteurs peuvent contribuer à la sous-utilisation des IAP et à l'image coercitive et stigmatisée des IAP qui se poursuit. Les psychiatres pourraient bénéficier d'une meilleure formation sur les IAP, et d'un auto-examen de leurs attitudes à l'égard des IAP et de leurs pratiques de prescription.

The rates of medication nonadherence are high in schizophrenia and other psychoses,[1–3] with significant negative consequences, such as relapse and rehospitalization.[1] An estimated 40% of the total costs associated with schizophrenia are attributed to rehospitalizations.[4] Using LAI antipsychotics is one of several strategies to enhance medication adherence among patients with psychotic disorders. However, in many regions of the world, and particularly in North America, very few people with psychotic disorders receive LAIs.[5–12] Attitudes of physicians toward certain types of treatments or treatment modalities may play a crucial role in shaping their prescribing practices,[13,14] and patients' acceptance of those treatments.[15] Thus attitudes of psychiatrists towards LAIs may contribute to the strikingly low use of LAIs for the treatment of psychotic disorders. Nevertheless, there have been, to our knowledge, only 6 studies (4 in Europe,[16–19] 1 in Australia,[20] and 1 in New Zealand[21]) investigating psychiatrists' attitudes toward LAIs and none in Canada. Most of these studies, with one exception,[16] found largely positive attitudes toward LAIs among psychiatrists. Notwithstanding such positive attitudes, most studies also found a gap between attitudes of psychiatrists and their practice, with relatively few patients being prescribed LAIs; a reluctance to prescribe LAIs in the early phases of psychotic disorders; and a continued perception of LAIs as being appropriate only for those seen as poorly adherent. So far, these few studies have predominantly used questionnaire or survey methodology. Much more nuanced information regarding physician attitudes toward LAIs (for example, subjective perceptions of advantages, disadvantages, and barriers to use) may be needed before planning any efforts to bring about more balanced attitudes. Therefore, our study investigated attitudes, beliefs, and perceptions held by psychiatrists regarding LAIs using focus group methodology.

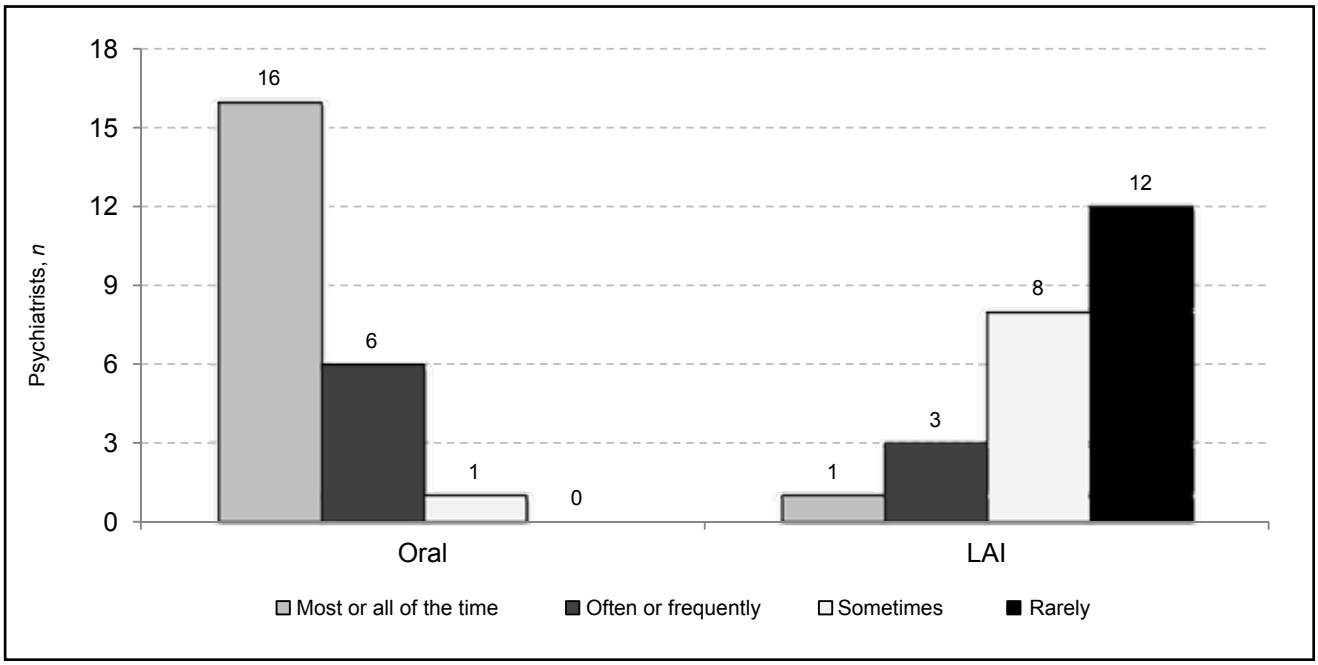
Clinical Implications

- The predominant use of LAIs as an end-of-the-road option, in a context of either coercion or a fragile therapeutic relationship owing to a history of treatment nonadherence, may continue to reinforce a negative image of LAIs.
- To increase the use of LAIs by physicians, systemic changes may have to be implemented to address pragmatic barriers of high costs, lack of storage facilities, and lack of trained staff to administer injections.
- Physicians may need better education about and increased familiarity with LAIs to improve use of LAIs.

Limitations

- A relatively small sample of psychiatrists participated in the focus groups, limiting the generalizability of the results. However, an attempt was made to include psychiatrists from 4 provinces in Canada.
- Important sociodemographic information (for example, years of experience) was not collected, which limits our ability to draw conclusions about possible influences on psychiatrists' attitudes about LAIs.

Figure 1 Frequency of prescription of oral and LAI SGAs



Method

Focus Group Participants

In 2010, 4 focus groups were conducted, 1 each in Halifax, Nova Scotia; Quebec City, Quebec; London, Ontario; and Victoria, British Columbia. Our study was approved by the relevant research ethics committees at each site. Specific attempts were made to recruit psychiatrists who treated patients with psychotic disorders, with the help of 4 coauthors (Dr Roy, Dr Tibbo, Dr Manchanda, and Dr Williams). No information was available about the actual prescribing practices or views of the psychiatrists who were invited to participate. Written informed consent was obtained from each psychiatrist. Psychiatrists were offered an honorarium for their participation. The final sample included 24 psychiatrists: 15 men and 9 women (5 from Halifax, 6 from Quebec City, 6 from London, and 7 from Victoria).

Focus Group Sessions

A focus group interview schedule with broad, open-ended questions regarding attitudes toward and prescribing practices around LAIs was developed. The focus groups lasted for 90 minutes, on average. All sessions were conducted by 2 trained facilitators; interviews were held in French at the Quebec site, and in English at the other locations. Psychiatrists were requested to fill out a brief questionnaire prior to the focus group about their typical practice setting and experience with LAIs. Participants were assured that the funding sponsor of the study had no role in the design of the interview schedule and data analysis.

Analysis

Frequency analysis was done with the pre-focus group questionnaire data. The focus group discussions were audiotaped, with the agreement of participants. The recorded material was fully transcribed. The transcribed data were analyzed by the sorting of verbatim material into themes, guided by the specific questions and topics that were probed for while concurrently allowing the data to suggest themes. Our accompanying paper (see Part I; Chaper 2; Iyer et al[22]) provides further details about our method of data analysis.

Results

Pre-Focus Group Questionnaires

Eleven (52.4%) psychiatrists reported working primarily in inpatient settings; 6 (28.6%) primarily in outpatient settings; and 5 (24%) in both in- and outpatient settings. Nine psychiatrists further described their setting: 5 reported working in both community and university settings; 1 in only a community setting; 2 in only a university setting; and 1 in only a forensic setting. Physicians indicated that they prescribed the oral formulation of SGAs most of the time (Figure 1) and that they had limited experience with LAIs. A majority (n = 21, 88%) had not personally administered an LAI AP and reported that a nursing staff member administered the injection in their work environment. The level of technical skill required to administer LAIs was perceived to be moderate by 17 psychiatrists (71%), high by 4 (17%), and low or none by 3 (12%). Nearly all psychiatrists in our study reported using LAIs with patients entering treatment both voluntarily and involuntarily. Only

1 psychiatrist (working in a forensic setting) reported using LAIs only with patients entering treatment involuntarily.

Focus Group Results

All of the analyzed data could be organized around 4 main themes: limited knowledge about and experience with LAIs, attitudes towards LAIs, prescribing practices around LAIs, and pragmatic barriers to using LAIs. Each of these categories is described below and illustrative quotations are presented.

Knowledge About and Experience With LAIs

A major theme that emerged was psychiatrists' lack of knowledge about LAIs (for example, available options, side effects, and outcome literature) and lack of confidence in extant knowledge. In this context, participants discussed their limited prior exposure to LAIs and how this possibly contributed to their low use of LAIs. Below are a few quotes illustrative of this theme:

> So another thing for me, personally, I haven't given one, for, since I was a resident . . . so I can't remember the last time that I did that, but I do know it was a very long time ago; there's a new injectable now . . . I wouldn't know where to start with it, so I need a bit of a learning curve to understand how to give them, to expect what the side effects were.
>
> I don't know that much about injectables, and I know that the new second-generation Risperdal is the only one I know is there, but maybe there's more that I don't know.
>
> If it's not being practiced by the consultants that you're training under, so then you're unlikely to kind of go that route.

Consistent with the results of the pre-focus group questionnaires, infrequent use of LAIs by most participants emerged as a theme. Pertinent quotations are, "I don't use that often," "I don't think I've initiated an LAI, ever," and "I might be able to count on my hand . . . "

Attitudes Toward LAIs

There were 3 important subthemes under attitudes toward LAIs: beliefs about patient perceptions regarding LAIs; personal bias against LAIs; and advantages and risks of LAIs.

Beliefs About Patient Perceptions Regarding LAIs. Psychiatrists had several beliefs about patients perceiving LAIs negatively, including the following:

1. Patients feel controlled or perceive LAIs as more intrusive or coercive.

   > I think there's a lot more control, at least it's perceived control, to them [patients], if they're on oral, because they decide whether they want to take it or not, but an injectable they have no option, if they don't take it we slam the CTO on them and they will have to take it, so there is no control. . . . unlike a pill they can manage themselves, with the injection they need somebody else to do it for them. So that's [an issue].
   >
   > And also, control. So if this stuff is inside me, I can't do anything about it, you know, there's a fear, something's taking over.

2. It is hard to convince patients to start an LAI.

   > Yeah, it's really hard to convince people to be on long-acting, but it's because you're trying to convince the people that are most challenging.
   >
   > They would rather be on oral medication and have cycles of admissions and readmissions and relapses . . . it takes sometimes a long time before people can accept injections.

3. Patients will refuse LAIs.

   > It's just a psychological thing, we, we just expect patients to say no, so you don't even . . .
   >
   > Nine out of ten are going to say no, if you give them the option, with all the information about lower amounts of medication going in, the greater safety of the long term, you can explain all of this, but nine out of ten people are going to say no.

4. Patients fear LAIs as they could hurt or be painful.

   > Sometimes patients, especially young patients have some fears associated with it . . . Could one of the fears be just simply the fear that something may go wrong in the injection? You know, ranging from it may hurt to how competent is the person giving the injection.
   >
   > There's some people who complain of pain.

5. Patients have strong feelings about the needle factor.

   > The struggle is the method, I mean, we wouldn't even be having this discussion, it's the method, it's the needle, the injection, and the dropping.

6. Patients see LAIs as a message from treatment providers that the patient cannot manage on his own or cope.

Personal Bias Against LAIs. Physicians' own negative views about injections or needles emerged as a theme. Interestingly, there was some awareness that this personal bias could be influencing prescribing decisions about LAIs. Below are some relevant quotations:

> If it was me, I would prefer the oral . . . certainly that's my own personal bias . . . And I'm sure that plays a role in whether or not I present it.
>
> If you've had injections, I hate them personally.
>
> I mean why should I offer an injection to somebody if they are willing to take an oral pill . . . why I am giving them the more painful, it's certainly not the option that I would want.
>
> Why would I take a needle, it's pain, so then, why would we?

Advantages and Risks of LAIs. There was often a clear acknowledgement of the advantages of LAIs. For instance,

a psychiatrist described his positive experience with LAIs, stating,

> Yeah, I've got about 30-some patients on injectable, I can tell you almost all of them . . . they see the benefits that they are much more stable than previously.

Other advantages of LAIs that participants discussed were "easy"; "psychiatrist has control as patients cannot be relied on for compliance or compliance cannot be understood from their presentation"; "easy to monitor"; "easy to ensure compliance"; "better outcomes"; "patients tend to continue seeing the good effects"; and "reliability, yeah, predictability."

There was some concern expressed about the irrevocability of an injection. "Two weeks it stays in the body, and something happens, dangerous . . ." and "One of the things with injectables, they're in there and you can't stop them the next day." Other concerns raised were about the side effects of LAIs (the idea that side effects of LAIs were greater than those of oral APs was occasionally brought up); the stigmatized nature of this treatment option; and the length of time for reaching a steady state with LAIs making them less suitable for the acute phase or in inpatient units.

Prescribing Practices Around LAIs

LAIs were generally seen as a more suitable option for patients in an involuntary context of either a CTO or a forced hospitalization or a threat of a CTO; patients with a clear history of nonadherence; and seriously ill patients, with risk factors for nonadherence, for example, "if the patient is using substances." Below is a pertinent exchange from one of the focus groups:

Facilitator: What type of patients would you consider an injectable for?

Doctor 1: Seriously ill patients, mostly.

Doctor 2: . . . mostly noncompliant . . .

Doctor 3: Yeah, the ones who look like they're going to be needing medication therapy for a long period of time.

Doctor 4: I would add not just symptomatology but also level of disability . . . if you're in fact going to be recurrently suicidal . . . or voices telling you to do something, a risk of being totally crippled . . . then certainly, for me I can justify in my own mind . . . what I would see as being the more forceful way . . . I'm going to put the medication into you, and that's all there is to talk about.

Some other quotations illustrative of this theme are:

> I see it as for involuntary patients so [my] brain shuts this option off for voluntary patients.

> Then they stop and then they come back in and you walk up to them and say we discussed this before, sorry, this is not up for discussion, you're going on injectable.

> You have to prove noncompliance first, then you think about the injections.

> I think it's funny; I think we might err on the side that they're going to be compliant, which makes no logical sense given the literature.

Regarding the treatment juncture at which LAIs were presented, LAIs were almost never seen as an option that could be presented early in the course of treatment:

> Yeah, I don't think I'll choose you know injectable antipsychotic as a first choice, I don't think anybody on the table will do that, it's only if they've had past failures.

Most physicians saw LAIs as a last resort after orals have been tried ("I'm aware that I don't think of injectables unless the oral is a problem, and I'm not sure why I do it that way") or as an option for the noncompliant patient after multiple relapses ("I'd say almost 100% of the time in my practice . . . patients after 2 to 3 or 4 repeat episodes is where I start LAIs"). LAIs were therefore never presented while first discussing medication options with patients:

> So I would certainly say that I would not introduce or even talk about a long-acting for someone who is coming to my clinic for the first time unless I believe that there is an adherence issue, that may be because of my own bias that injectables are painful or that the therapeutic alliance will be damaged.

The only exception to this was presented by a psychiatrist working in a forensic setting. LAIs were also generally considered unsuitable during the early treatment course of psychotic disorders.

Pragmatic Barriers to Using LAIs

Another theme that emerged pertained to pragmatic barriers to the use of LAIs: "I think not all the time, but there are practical issues that even hold me back from suggesting it, a lot of the time." These included problems with storage and lack of personnel to administer injections in small towns and (or) small centres; difficulties finding trained and available nursing staff to give injections; cost considerations (even when patients were covered for the cost of the LAI, sometimes physicians perceived LAIs as expensive and as costing the Canadian health care system); concerns about arranging injections when patients went on vacation; and difficulty transferring care to general practitioners who may not be comfortable with LAIs. Below are some appropriate quotations:

> I can't get anybody to give injection to my patients.

> Every town needs a facility or two.

> A lot of the small centres don't even touch the injectables.

> You know one can say that the patient comes first, and you shouldn't think of it, but you are working in the health care, finite amount of dollars, and I do think that to a certain extent it is our responsibility to try and balance what's best for the patient with

what is also available, 'cause if in fact you spend so much more of this, then you're going to get patients who get less service, so is that fair either?

I am much more aware of, the cost in contrast, you know when I sit and do the sums. I have 30 mgs of olanzapine a day, I don't think twice about it, and that is very clearly exactly the same cost, but in my forebrain is [that Risperdal] Consta [risperidone LAI] is expensive.

If you are travelling abroad for a month, you can't carry your Consta with you. . . .

But say . . . I offered that my first line was an injection, suddenly I've increased the workload of colleagues . . . when there's a nurse [who's] scheduled to do the injection and when they're off sick, or they go on vacation, the struggle they have finding someone to do that if I'm increasing that load, there might be a challenge. Even unconsciously, I'm aware of it now, but I might avoid it because I don't want to create a lot of stress with my colleagues.

Discussion

Our qualitative study yielded insights about physician-related factors, such as lack of information and (or) misinformation about LAIs; limited experience with LAIs; beliefs about patients' perceptions of LAIs; personal biases against injections; and the viewing of LAIs as being appropriate for only certain types of patients. These, along with pragmatic barriers, could explain the underuse of LAIs in the treatment of psychotic disorders in Canada. Although some psychiatrist-participants had questions about the side effects and outcomes of LAIs, note that most among them discussed various advantages of LAIs. To some extent, there seems to be a discrepancy between this acknowledgement of advantages of LAIs and their limited use. This is consistent with previous surveys of physician attitudes regarding LAIs.[19,21] There may also be a historical context surrounding current perceptions about and the low use of LAIs. Thus focus group participants spoke about "the paradigm shift in terms of our views about the LAI" that happened along with the mass switch from FGAs to SGAs that were available only in oral form until recently.

Our study suggests that LAIs may generally be presented by psychiatrists very late in the course of treatment, often after an established pattern of nonadherence and relapses, and in the coercive context of a CTO or the threat of one. This prescribing context may further perpetuate the coercive and stigmatizing image of LAIs, and such an image, in turn, may prevent physicians from presenting it as an option early on to patients. To optimize the use of LAIs, it is critical that physicians reflect on this vicious circle surrounding prescribing practices of LAIs.

Physician beliefs regarding patient perceptions about LAIs emerged as an important theme in our analysis. Examining together the findings from our patient (see Part I, Iyer et al[22]) and physician focus groups, there were similarities between physician and patient perceptions regarding the pragmatic disadvantages of LAIs and regarding the high costs and inconveniences associated with clinic appointments and travel arrangements. While physician-participants emphasized on the pain-and-needle factor, only 2 patients with no experience with LAIs and none of the patients currently on LAIs saw this as a salient disadvantage of LAIs. Nearly all psychiatrists in our study assumed that patients would refuse LAIs or that presenting the LAI option would negatively impact the therapeutic relationship. Therefore, they saw LAIs as an option for the noncompliant patient. However, our patient focus group study and the study by Heres et al[23] suggest that a not insignificant minority of patients may consider LAIs as a suitable option for better managing their illness and reducing the risk of relapse, and for the convenience of not having to remember to take pills every day. Further, at least one patient in our study expressed that she would have liked to be presented the LAI option much earlier in the course of treatment. The findings from the physician focus groups suggest that physicians may tend to discount the evolution in attitudes regarding LAIs among patients. There was very little awareness among physicians that patients may have favourable attitudes regarding LAIs, such as seen in our patient study and in other such studies.

While the views of the patient participants in our study do not represent the entire range of patient attitudes toward LAIs, our findings suggest that, in many if not all instances, there may be a lack of correspondence between physician beliefs regarding patient perceptions and patients' own perceptions. This lack of correspondence suggests that physicians ought to effectively inquire about and listen to what patients say about LAIs in particular and other treatment in general. Such an approach would be congruent with a patient-centred, shared decision-making[24,25] approach to treatment. There may be a continuously interacting dynamic between physician and patient attitudes.[26–29] Thus how physicians perceive LAIs and what they believe about their patients' negative perceptions regarding LAIs may possibly even contribute to the actual negative perceptions of patients about LAIs. Future studies are needed to systematically examine this proposition.

The results of our study suggest a need for better education and updating of skills around LAIs among psychiatrists, ideally in a context that allows examination of attitudes (for instance, via academic detailing[30–32]). Even though the purpose of our focus groups was merely an exploration of attitudes and experiences with LAIs, interestingly, it provided to some of the physician-participants an opportunity to reflect on their own attitudes and prescribing practices:

> I'd be interested to see my own biases as to why that [LAIs] is not an option in own practice.
>
> Yeah, so what I immediately thought was well whoever would choose it? . . . But I realize that I don't even bring it up. So that's kind of my learning piece here tonight . . . You know, why don't we just put it out as options?

Concerted efforts need to be made to address pragmatic barriers so that treatment choices are less influenced by these considerations.

Our study has several limitations. We had a relatively small sample of psychiatrists (4 groups). Nonetheless, our sample included 4 Canadian provinces. The limitations of our recruitment strategy must be acknowledged. However, no attempt was made to screen or invite psychiatrists based on their views or prescribing practices about LAIs. Unfortunately, we did not collect some important demographic information from our psychiatrist-participants, such as years of experience, age, and percent of patients with psychotic disorders in their practice. Despite these limitations, our study begins to fill a crucial knowledge gap regarding physician attitudes about LAIs in Canada. It also highlights the usefulness of qualitative research methods[33,34] in understanding prescribing practices in psychiatry.

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Chapter 4

Long-Acting Injectable Antipsychotics: Recommendations for Clinicians

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A major source of limitation to the real effectiveness of antipsychotics is the high rate of patient nonadherence or, more frequently, partial adherence. Using long-acting injectable (LAI) formulations is likely to reduce the impact of such adherence problems. Conversely, the use of LAIs in Canada remains low relative to many other jurisdictions.

Based on effectiveness data from randomized control trials and other, less rigorous, studies, as well as our 2 qualitative studies exploring numerous issues around the use of LAIs, including their low use, we put forward 10 different recommendations for consideration by clinicians. These are also based on the experience of many clinicians and clinician scientists. These recommendations address mostly clinical challenges associated with the use of LAIs. Their application in clinical settings is illustrated in our report through several case examples highlighting the large variation across patients and different phases of illness. It is recommended that LAIs should be considered as a treatment option for psychotic disorders across all phases, including the first 2 to 5 critical years.

Antipsychotiques injectables à action prolongée : recommandations aux cliniciens

Une source importante de limitation de l'efficacité réelle des antipsychotiques est le taux élevé de non-observance ou plus souvent, d'observance partielle des patients. Recourir à des formules injectables à action prolongée (IAP) est susceptible de réduire l'effet de ces problèmes d'observance. À l'inverse, l'utilisation des IAP au Canada demeure faible relativement à de nombreux autres pays.

Selon les données d'efficacité tirées d'essais randomisés contrôlés et d'autres études moins rigoureuses, ainsi que de nos 2 études qualitatives explorant de nombreuses questions liées à l'utilisation des IAP, y compris leur faible utilisation, nous présentons 10 différentes recommandations aux fins d'examen par les cliniciens. Celles-ci sont également basées sur l'expérience de nombreux cliniciens et scientifiques cliniciens, et abordent surtout les problèmes cliniques associés à l'utilisation des IAP. Leur application en milieu

clinique est illustrée dans notre rapport par plusieurs exemples de cas mettant en évidence la vaste variation entre les patients et les différentes phases de la maladie. Il est recommandé de considérer les IAP comme option de traitement pour toutes les phases des troubles psychotiques, y compris les 2 à 5 premières années cruciales.

Antipsychotics are essential but not sufficient for management of a psychotic disorder, and inclusion of other treatment strategies, such as family intervention, CBT, case management, and addictions treatment, is almost invariably necessary. The weight of the evidence regarding the use of APs suggests that LAIs are as effective as oral APs, and, in many cases, may improve rates of remission. They can decrease risk of relapse, hospitalization, or disengagement from services, as well as other health and social consequences of inadequate treatment of psychotic disorders. Given that the nonadherence to APs is a recurring problem throughout the course of illness for many patients, and that these rates are particularly high during the critical period of the first 2 to 5 years,[1] when long-term trajectories of clinical and social outcome are established,[2,3] consideration of offering and using LAIs during all phases of the illness is recommended.

In the previous 3 chapters of this supplement, we have reviewed different levels of evidence regarding the efficacy, effectiveness, side effects, and use of SGA LAI medications and results from our 2 interconnected qualitative studies on LAIs. The latter were designed to explore perspectives of patients and psychiatrists on issues related to the use of LAIs as a treatment choice for psychotic disorders. These results have also provided some information regarding possible reasons for relatively low use of LAIs in Canada. In this final chapter of the supplement, our objective is to provide recommendations for a rational use of LAIs as part of pharmacological treatment of psychotic disorders. We have deliberately kept the focus of our recommendations on clinical and practical issues and provided case examples to illustrate the use of some of the recommendations made as well as limitations in the use of LAIs. For details of effectiveness and side effects of oral and SGA LAIs, the reader is referred to the first report in this supplement (see Chapter 1; Manchanda et al[4]).

We, therefore, recommend to clinicians the following in relation to offering LAIs as one of the choices of treatment to patients with a psychotic disorder:

Clinical Implications

- The recommendations are oriented toward routine clinical practice in the management of psychotic disorders as illustrated by case examples and should, therefore, be of practical use to clinicians.
- These recommendations may improve rates of LAI use, which currently are significantly lower in Canada, compared with some other countries.
- Greater use of LAIs, especially during early course of psychotic disorders, may prevent relapses in vulnerable patients, prolong periods of remission, and facilitate engagement in psychosocial interventions and rehabilitation in patients otherwise unlikely to engage in these aspects of treatment.

Limitations

- As the evidence of superiority of LAIs is, at best, equivocal, the recommended higher use of LAIs may be subject to debate.
- The lower use of LAIs may be influenced by clinicians' prior training and exposure and negative attitudes toward LAIs.
- Using LAIs does not completely assure improved adherence in the long term and some patients may relapse despite being on LAIs.

1. For All Phases

The existence and potential use of LAIs for AP therapy should be discussed with patients and families at all phases of illness, including the critical period[1] of the first 2 to 5 years.

2. Informed Patient Decision

Information regarding LAIs should be carefully and systematically discussed with patients in a collaborative environment, taking into consideration patients' and their families' views regarding such use. Such information should be reviewed on a regular basis, especially if there are unresolved issues regarding adherence to treatment or suboptimal response to oral medication related to partial adherence. In all cases, patients' opinion about the choice of an LAI should be considered regarding knowledge of its effectiveness, ease of administration, frequency of injections, and cost. This may also present an opportunity to provide further information to patients to assist them in making an informed decision.

3. Clinical Stability and Patients' Change in Opinions and Attitudes

Psychiatrists and other clinicians should be prepared to see patients' attitudes toward medication, issues related to adherence to treatment, and need for LAIs as protean and not static phenomena. After a period of stability, patients may develop a different and more positive attitude toward their treatment, experience an improved therapeutic relationship, and be in a better position to evaluate their options of oral, compared with LAI, medications. Hence continued discussion regarding various formulations of medications is recommended.

4. Physicians' Knowledge and Attitude

Psychiatrists and other clinicians treating patients with psychotic disorders should be well informed and trained in the use of LAIs. Results from our qualitative studies, reported in this supplement, confirm an observation that many mental health clinicians may have a bias against LAI therapies, and believe that patients are likely to reject such avenues of treatment. We recommend that clinicians should be aware of such attitudes and bias and should attempt to correct them. For example, psychiatrists and treatment teams should not assume rejection or ubiquitous fear of needles regarding the use of an LAI as the most likely response from patients at any stage in the course of illness. This may allow the clinician to present an LAI as an option on repeated occasions.

5. Nonadherence

In case of overt or impending nonadherence to medication, serious consideration should be given to using LAIs as one of the choices for addressing nonadherence. Many patients are assumed to be adherent (at times mistakenly) by their treating clinicians. LAIs should be considered and discussed in circumstances where there may be conflicting evidence or uncertainty about adherence to oral medications.

6. Involuntary Treatment During Acute Phase Psychosis

It is acknowledged that during periods of acute psychosis, some patients refuse treatment altogether and (or) specifically refuse AP medication. Under such circumstances, it is recommended to discuss using LAIs as an option with the patient and provide detailed information regarding their effectiveness, including side effects, as well as potential advantages individualized for the patient. However, clinical realities, at times, demand involuntary hospitalization and treatment, within the provisions of the respective provincial mental health legislation, often in the interest of preventing injury or harm to the patient or others. In such situations, almost invariably, the use of LAIs becomes necessary. However, after initiating treatment with an LAI under such coercive circumstances, it is recommended that information regarding the use of LAIs be again discussed with the patient (and family where appropriate) early in the course of long-term treatment in an outpatient or community setting, and the specific conditions that may have dictated the initiation of an LAI be acknowledged. This may allow the patient to express their views about the risks and benefits of continued use of an LAI. This is based on the findings from the patient qualitative study reported earlier in this supplement (see Chapter 2; Iyer et al[5]).

7. Engagement With Psychosocial Interventions and Rehabilitation

Advantages of the use of LAIs, whether initiated under coercive or persuasive circumstances, must be shown to facilitate efforts at engaging the patient and their family in other nonpharmacological treatments (for example, family intervention, CBT, and supported employment) and rehabilitative efforts. This is likely to assist the patient in pursuit of goals they define in collaboration with their clinician.

8. Oral Supplementation and Stabilization

While it is preferable to initiate treatment with an oral AP, it is not necessary to achieve stabilization with oral medication prior to initiating an LAI, especially if the patient is refusing to take oral medication or unlikely to take it regularly during the acute phase of psychosis, as long as the patient has been exposed to a test dose. This may be particularly relevant to patients being treated for their FEP.

9. Monitoring

While each patient needs to be assessed at the time of every injection, regular detailed evaluations of the effectiveness and side effects should be conducted at a minimum rate of every 3 months. Side effects to be evaluated should include movement disorder extrapyramidal side effects, tardive dyskinesia, and akathisia), metabolic (blood pressure, weight, glucose, and lipids), and signs of hyperprolactinemia. Results of such evaluations should be discussed with patients so as to allow them to make further choices regarding medications.

10. Special Situations

Clinicians should be prepared to proactively address situations that may arise, such as pregnancy, travel, moving, medication coverage, age (transfer to geriatric services from adult or to adult from child psychiatry), which may lead to a change or interruption in therapy.

Case Reports

The following is a sample of case reports demonstrating variations in conditions under which LAIs are prescribed and the limitations associated with their use:

Case #1

A 22-year-old man, following initial refusal and with the help of his overwhelmed family, accepted oral medication after 3 weeks of hospitalization for an FEP. Despite his initial fears of needles and injections, following a week of counselling and education, with the help of his family, he accepted to take an LAI. During this period, he reluctantly accepted case management within the EI service. Within a couple of months, he achieved remission of hallucinations and delusions and significant improvement in disorganization symptoms. Fearing to be stigmatized, he refused social assistance and, despite significant coverage by the government insurance plan, he had to pay a monthly fee for his LAI, which he refused to continue after only a couple of months. Despite temporary respite through free samples of LAIs and assistance from a hospital fund, he refused further treatment and follow-up after 8 months.

Following 6 months of total nonadherence to all aspects of treatment in the EI service, he was returned to the

hospital emergency department with a relapse of psychotic symptoms, disorganization of thought, bizarre behaviour, and risk of suicide. The patient continued to refuse medication, convinced that his symptoms were secondary to cannabis misuse 6 months prior to admission. Following 3 weeks of refusal to take medication, a court order for treatment was requested and granted for 2 years specifying use of a monthly LAI. Within 2 weeks, following significant improvement in his psychotic symptoms and behaviour, he was discharged to be followed up intensively again in the EI service. Two months later, the patient showed remission of positive symptoms following a dose increase and remained in that state for the subsequent 2 years.

This case illustrates the possibility of initiating an LAI very early in treatment following hospitalization for an FEP, the importance of family support and the necessary collaboration between the treatment team and the family, the issue of cost interfering with continuation of the LAI, and the importance of access to a comprehensive treatment program for follow-up. The cost may have been a serious deterrent for the patient to continue the LAI and may have resulted in stopping treatment altogether for 6 months. The patient was flexible enough to resume care with enthusiasm, even after having dropped out of treatment for long periods of time.

Case #2

A 23-year-old, single, unemployed man, with 2 previous admissions, with a diagnosis of psychosis not otherwise specified and history of persecutory delusions, disorganized behaviour, and possible hallucinations, as well as cannabis abuse, was assessed as an outpatient. His continued family support was provided conditional on his having mental health follow-up and acceptance of treatment, as well as abstinence from drug use. He had been treated previously with olanzapine, orally, with quick response to medication but had discontinued treatment shortly after his FEP. Referral information suggested poor or intermittent adherence, despite the supervision of his cousin. He was free of active symptoms of psychosis at assessment and denied continuing drug use, despite evidence to the contrary. Although denying nonadherence, he did agree to change his medication to an LAI. Attempts to link him to a psychoeducational program were partially successful. He attended his monthly injections for the first 4 months, often requiring reminders. He then refused any further injections and insisted on oral medications. He reported no adverse effects while on an LAI. Family reported likely ongoing cannabis and alcohol use. He attended 3 further visits, accepted repeat prescriptions for oral medication but then discontinued treatment altogether and returned to his native country following breakdown of family support, which was contingent on his accepting treatment.

This case illustrates that the risk of relapse is further enhanced by cannabis abuse, as is reluctance to take medication. Only under pressure from family did the patient accept an LAI, but not for long. It is possible that the coercive element of having to accept treatment under such circumstances did not work in his case and that the patient never engaged with the treatment team. Other factors, such as being away from his native country and immediate family, may have diluted his enthusiasm to stay involved in treatment and in this country. It raises possible issues related to cross-cultural concepts of mental illness and the need for treatment that is sensitive enough to such issues and the involvement of immediate family. It is possible to speculate that had LAIs been introduced during the initial episodes, the patient may have achieved longer stability and been more adherent to long-term treatment.

Case #3

A 30-year-old woman, with 5-month history of joblessness and psychotic symptoms (hallucinations and persecutory delusions) leading to dangerous behaviour resulting in serious injury and little or no negative symptoms, was evaluated by the hospital EI service and treated with oral APs. Within 3 weeks after discharge and following excellent response to medication, she began to express doubts about the role of medication in her recovery from the episode of psychosis and was persuaded to take an LAI AP. Despite increments in dosage of the LAI, she continued to be preoccupied by past delusions and displayed significant anxiety. Admitted to the hospital for a short duration, she accepted higher doses of the LAI medication, and remained stable for the next 3 months. Though she is still convinced of past delusions, she is no longer preoccupied or distressed by them. She is also less socially isolated and has plans for the future.

This case reminds us, as do some of the other cases, the potentially life-threatening nature of untreated psychotic disorders and the need to evaluate, very early in course of the illness, patients' likelihood of continuing with oral medications. Reluctance to take medications at the onset of treatment is associated very strongly with future nonadherence.[6] In this case, discussion of an LAI was introduced very early on and the patient was persuaded to try this approach, but only in the context of a comprehensive plan of care through an intensive case management program.

Case #4

A 21-year-old homeless man was hospitalized after having demonstrated extremely disorganized and bizarre behaviour leading to detention and charges for offences for which he was considered not criminally responsible. He had been a regular and heavy user of cannabis. The court ordered his release on the condition that he would comply with his medications and follow-up treatment. He was accepted in the EI service and began to work with his case manager. He had limited or no insight into the nature of his psychiatric problems but was interested in improving his living conditions and bringing some stability to his life. While in hospital, after a relatively limited response to oral APs, he was persuaded to take an LAI as it was obvious that given his lack of understanding of the need

for medication and his lifestyle, he would have difficulty in maintaining a regular oral medication regimen. However, this was tied with providing him basic assistance, ranging from accommodation in a small apartment, utensils and furniture, and assistance in management of his funds from social assistance. In the absence of any family involvement, and with the assistance of a community worker as well as his case manager in the EI service, he agreed to the above arrangement. Under this arrangement of a modified assertive case management, he followed the recommendations and remained out of the hospital for more than 1 year. He is now beginning to contemplate further steps toward resuming his education and remains under the initial court order. He continues to use cannabis, albeit considerably less, and still presents with some negative symptoms, such as amotivation and avolition.

This illustrates a very different but not uncommon situation of a young man disconnected from family and friends ending up in the legal system because of behaviour associated with untreated psychosis. In this case, the patient accepted an LAI within the context of not only a court order but also, and equally important, with the potential of being helped with basic things in life, such as accommodation, furniture, facilities to cook and eat, and assistance with controlling his meagre finances to reduce his cannabis use and allow him to spend more money on food. Note that this patient never accepted the diagnosis of a psychotic disorder but accepted an LAI as part of a larger package that assisted him with resumption of a basic standard of living, without having to be homeless. It is very likely that a court order on its own would not have persuaded the patient to cooperate with his treatment had it not been combined with the approach taken.

Case #5

A 62-year-old single man, with a 30-year history of schizoaffective disorder, had worked until the age of 50 when he had been hospitalized several times during an 8-year period with persecutory delusions and auditory hallucinations and episodes of manic and, at times, self-destructive behaviour. Persuaded by his clinician about the seriousness of his tendency to nonadherence to oral medications, he agreed to start an LAI. He relapsed, despite regular use of an LAI. He was eventually convinced to start and adhere to a clozapine protocol and was treated with a maximum tolerated dosage of 300 mg/day in addition to the biweekly LAI. No further increase was possible, given the side effects (sialorrhea, constipation, and sedation, all of which subsided).

With no particular trigger, he relapsed a year ago. He was started this time on a monthly dose of a different SGA LAI, while the dose of clozapine was maintained. He responded well to treatment and no longer suffers auditory hallucinations or delusions. He plays golf, bowls, drives, shops, goes out to restaurants, and visits family. Based on data from regular monitoring, he has shown significant weight gain, with a body mass index in the preobese range, but there is no indication, thus far, of any glucose intolerance, dyslipidemia, or hyperprolactinemia.

This example shows how even a later-onset psychotic disorder can be difficult to manage primarily as a consequence of nonadherence to oral medication, resulting in multiple episodes and eventually treatment refractoriness. Treatment with clozapine, while necessary, was restricted because of the patient's intolerance of a higher dose. Adding an LAI, with prior knowledge of patient's reluctance to take oral medication, facilitated a greater degree of clinical stability. The patient agreed to take the LAI voluntarily after considerable discussion and persuasion. While there is little empirical evidence to support such combination, at times it becomes a matter of clinical prudence, while at the same time requiring a very close monitoring of progress and adverse events. We are not recommending such combination but simply illustrating practical problems in managing difficulty clinical situations.

Case #6

A 45-year-old mother of 2 young children, who works at odd manufacturing jobs to avoid the stigma of being on welfare, was diagnosed with paranoid schizophrenia 20 years ago. Her medical history includes obesity, iron-deficiency anemia, and periods of hypokalemia. Her relapses, most often owing to nonadherence to oral medication, lead to hospitalizations, and consist of irritability, complete isolation, excessive religious preoccupation, and fasting leading to dehydration and hypokalemia. After several relapses, she was persuaded during hospitalization by the nursing staff and family to agree to start an LAI initially along with olanzapine, 15 mg/day. She responded very well and reached remission within 3 months. Not long after discharge, she stopped her oral medication because of weight gain and then refused to meet with the nurse or accept home visits for her LAI. This scenario was repeated several times, resulting in 5 hospitalizations in the last 7 years. During the last hospitalization, 1 year ago, her husband threatened to separate if she discontinued her injection again. The family agreed that if she discontinued her LAIs, a treatment order would be requested. She has been adherent with an LAI ever since and has continued to receive support and encouragement from the treatment team. Although her husband has returned to their native country, during the past 15 months she continued the LAI, has remained in remission, and works full time, cares for her children, visits some friends, and attends church weekly.

Finally, this case illustrates the potentially dangerous medical consequences of an untreated psychotic disorder, exacerbated by nonacceptance of, and nonadherence to, an AP. In a case such as this, with multiple relapses, LAIs would be the obvious choice to be discussed, with the hope to persuade the patient to accept such an approach to treatment. In this case, it appears that the threat of separation and loss of custody of children may have eventually contributed to her voluntary acceptance of an LAI. It is also noteworthy that after a period of stability

on the LAI and resumption of almost all roles in her life, she continued the LAI, even though her husband left. It is possible that a sustained experience of an improved quality of life allowed her to evaluate her options more rationally. It is also possible that initial combination of oral and LAI may have exacerbated side effects, such as weight gain, and an earlier cessation of oral olanzapine may have encouraged the patient to remain on the LAI only.

Discussion and Conclusions

The above brief case reviews illustrate the seriousness of psychotic disorders for people's lives and the need for adequate treatment. They also show variation in circumstances related to initiation of LAIs at different points in the course of psychotic disorders, influenced by personal, social, and family circumstances, a collaborative relationship with the treatment team, appropriate use of different legislative statutes available, and, most importantly, the patient's involvement at any stage in a treatment program that offers psychosocial interventions as well as opportunities for different aspects of recovery.

We have presented a set of recommendations for the rational use of LAIs as a treatment option in the management of psychotic disorders. The recommendations are based on an extensive review of the literature, on the qualitative studies we conducted to explore possible reasons for underuse of LAIs, and on the clinical expertise of numerous clinicians and researchers. While we have tried to supplement the recommendations with a few case examples, not all issues contained in the recommendations have been possible to be thus demonstrated. In particular, we have tried to illustrate the importance of an open dialogue between the patient, family, and the clinical team under different circumstances and at all stages during the course of illness, including the first crucial 2 to 5 years. The latter period is important as most of the long-term trajectories, including treatment refractoriness, are established in this rather critical period. The importance of these recommendations was highlighted by data obtained from the patients' focus group study (see Chapter 2; Iyer et al[5]).

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Abbreviations

AE	adverse event
AP	antipsychotic
CBT	cognitive-behavioural therapy
CTO	community treatment order
EI	early intervention
EPS	extrapyramidal symptom
FEP	first-episode psychosis
FGA	first-generation antipsychotic
HRQoL	Health-Related Quality of Life
LAI	long-acting injectable
NNT	number needed to treat
PANSS	Positive and Negative Syndrome Scale
PEPP	Prevention and Early Intervention Program for Psychoses
PLAI	paliperidone palmitate long-acting injectable
OLE	open-label extension
RCT	randomized controlled trial
RLAI	risperidone microsphere long-acting injectable
RR	relative risk
SGA	second-generation antipsychotic

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