Attitudes of Psychiatrists Toward Antipsychotic Depot Medication

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Background: Since 2002, a second-generation depot antipsychotic has been available that potentially combines the advantages of depot administration and the favorable aspects of the so-called "atypical" antipsychotics. Nevertheless, long-acting injectable formulations are seldom prescribed in the treatment of schizophrenia.

Method: We surveyed 350 psychiatrists at an international conference as to their reasons for not prescribing a first- or second-generation depot antipsychotic for their patients diagnosed with schizophrenia or schizoaffective disorder.

***Results*:** The most important factor opposing depot prescription pertaining to both classes is a presumed sufficient compliance with oral antipsychotic treatment. First-generation depots are avoided due to the threat of extrapyramidal side effects, whereas second-generation long-acting injectable drugs are considered to be associated with high treatment costs. Less than 36% of participants' patients have ever been offered antipsychotic depot treatment.

Conclusion: Aversions to prescribing depot treatment are frequent among psychiatrists and appear to be unrelated to the antipsychotic class. The stated reasons for not prescribing depots are generally not supported by the current evidence, and further studies are urgently needed to clarify the advantages of depot treatment.

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Since the development of depot treatments in the 1960s, their advantages in the relapse prevention of schizophrenia have been demonstrated for first-generation antipsychotics (FGAs) in several studies yielding both diminished rates and reduced durations of rehospitalization.[1] Other favorable aspects of depot formulations are stable plasma levels, a pattern of regular contact with the health care system through the injection schedule, and the facilitation of compliance with the medication.[2] In spite of these advantages, depot antipsychotics play a minor role in the treatment of schizophrenia and are afflicted by a number of prejudices. Data from a survey in southeast England highlighted the negative image of antipsychotic depot treatment in schizophrenia at a point in time when only oral second-generation antipsychotics (SGAs) were available.[3] British psychiatrists stated that depot antipsychotics are old-fashioned, stigmatizing, and less acceptable to both patients and their relatives than are oral compounds. On the other hand, depot antipsychotics were considered to be compliance enhancing and highly preventive of relapse. The authors of the British survey concluded that psychiatrists would consider depot treatment more favorably if a long-acting injectable SGA drug were available, presumably because they would consider it to have a lower incidence of side effects.[3]

By now, the expected amelioration of extrapyramidal side effects,[4,5] as well as the somewhat superior efficacy in both acute episodes[6] and relapse prevention[7] of oral SGAs, has been demonstrated in several studies. Consequently, up to 4 of 5 patients discharged from hospitals in 2001 had been treated with these new compounds.[8] In 2002 and 2003, the second-generation long-acting injectable antipsychotic risperidone microspheres became available in the United States and several countries in Europe. In contrast to former long-acting injectable formulations, the risperidone microspheres are an isotonic, water-based suspension and therefore not literally a depot, but will be called a depot further on in this article to simplify matters. Up to now, we have not known in detail why psychiatrists do not prescribe a depot formulation and whether there is a difference in reasons coinciding with the class of antipsychotic drug. In order to highlight the current attitude toward long-acting antipsychotics, we

surveyed psychiatrists as to their reasons for not assigning depot treatment to patients diagnosed with schizophrenia.

METHOD

At the eighth World Congress of Biological Psychiatry (June 28–July 3, 2005, Vienna, Austria), we questioned 350 psychiatrists attending a symposium about their attitudes toward depot antipsychotic treatment (questionnaire available through first author upon request). Demographic data covered the age of the psychiatrist, gender, country of current occupation, length of experience in the psychiatric field, type of institution (university clinic, routine care clinic, or private practice), and official function at the institution. Furthermore, each psychiatrist was to estimate what percentage of the total number of patients treated so far in the year 2005 had been diagnosed with schizophrenia or schizoaffective disorder. Within this patient group, the percentages of patients treated with SGAs and of patients receiving an antipsychotic depot treatment were obtained.

The participants were to rate to what extent 16 statements on depot antipsychotics influence their decision against the prescription of a long-acting formulation in the treatment of a patient diagnosed with schizophrenia or a schizoaffective disorder. The degree of influence on the decision against depot treatment was rated on a 5-point scale (see Figure 1 footnote). We considered a minimum mean rating of "3" in either the FGA or SGA category as threshold for the potential impact of a statement on a psychiatrist's decision against depot treatment. For statements meeting this criterion, we also listed the percentage of applicable participants, i.e., those psychiatrists who scored 3 or higher. Each statement was rated for first- and second-generation depot antipsychotics separately. The item "patient needs an antipsychotic not available as depot formulation" left the additional possibility of naming applicable drugs. At the end of the statement list, we asked for further factors contributing to the decision against depot treatment in an open question. Finally, the psychiatrists estimated what percentage of their patients currently taking oral antipsychotics had ever been offered a depot treatment by the psychiatrist. In addition, we checked for a dependence of the difference in the frequency of prescriptions of SGA and depot antipsychotics on the age of the psychiatrist and whether he or she was independently working in a private practice or employed in a clinic.

Statistical Analysis

Differences between means in the various categories (e.g., age of psychiatrist, setting of treatment) were checked with the t test for unpaired samples with 2-sided levels of significance, as stated in the Results section. Means of ratings per statement were checked for differences between FGAs and SGAs, using t tests for paired samples. To determine whether performing t tests was the appropriate method, a Q-Q plot of the differences in the ratings per statement between second- and first-generation depot antipsychotics was performed that—on inspection—showed no deviation from the normal distribution. The 2-sided level of significance of $p < .05$ was Bonferroni adjusted for multiple testing to $p < .003$. Data were analyzed using SPSS Version 12.0 for Windows (SPSS Inc.; Chicago, Ill).

Table 1. Demographics of Participating Psychiatrists

Characteristic	Value, N[a] (%)
Gender	
Female	83 (33.9)
Male	162 (66.1)
Nationality	
German	241
Swiss	1
Institution	
University	13 (5.4)
Clinic	77 (31.8)
Private practice	152 (62.8)
Position	
Junior resident	5 (2.1)
Senior resident	8 (3.4)
Head of department	46 (19.6)
Head of a clinic	26 (11.1)
Independent physician	150 (63.8)
	Mean (SD)
Age, y	
Female	46.7 (7.8)
Male	48.7 (7.4)
Length of experience in the psychiatric field, y	18.07 (7.7)
Diagnosed as F20.x or F25.x,[b] % of patients	26.2 (17.1)
Oral SGA, % of patients	74.3 (24.4)
Depot antipsychotics, % of patients	19.5 (15.1)
Ever offered a depot treatment, % of patients	35.5 (22.1)

[a]Not all participants answered every question.
[b]F20.x and F25.x signify schizophrenia and schizoaffective disorder, respectively (ICD-10 criteria).
Abbreviation: SGA = second-generation antipsychotic.

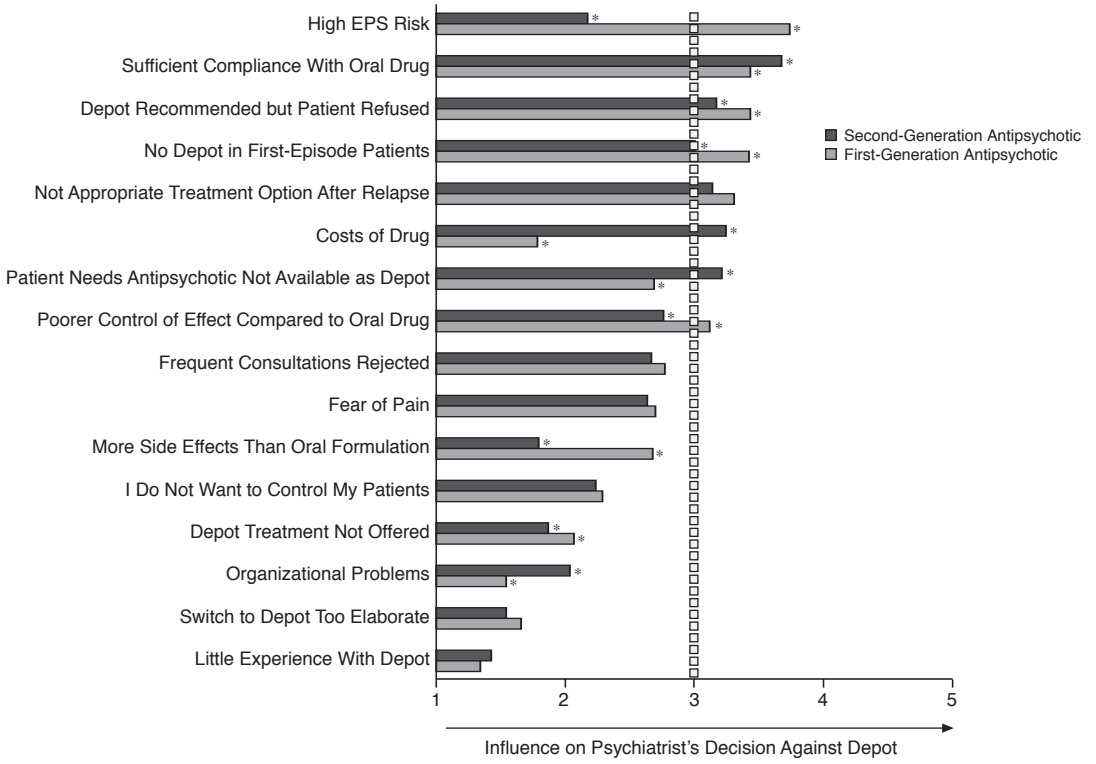
RESULTS

A total of 246 (70.3%) of the 350 psychiatrists returned the completed questionnaire. Demographic data are shown in Table 1. Most of the participants were independently working in a private practice (62.8%) and less than 50 years of age (57.1%). Of those patients treated by the participants who were diagnosed with schizophrenia or schizoaffective disorder, 74.3% (SD = 24.4%) were treated with an oral SGA, and 19.5% (SD = 15.1%) were currently taking a depot formulation of an FGA or SGA. The possibility of a depot treatment was only ever offered to 35.5% (SD = 22.1%) of the patients.

Statements With a Potential Impact on the Psychiatrist's Decision

As described above, we first identified those items that had a potential impact on a psychiatrist's decision against

Figure 1. Mean Rating per Statement[a–c]



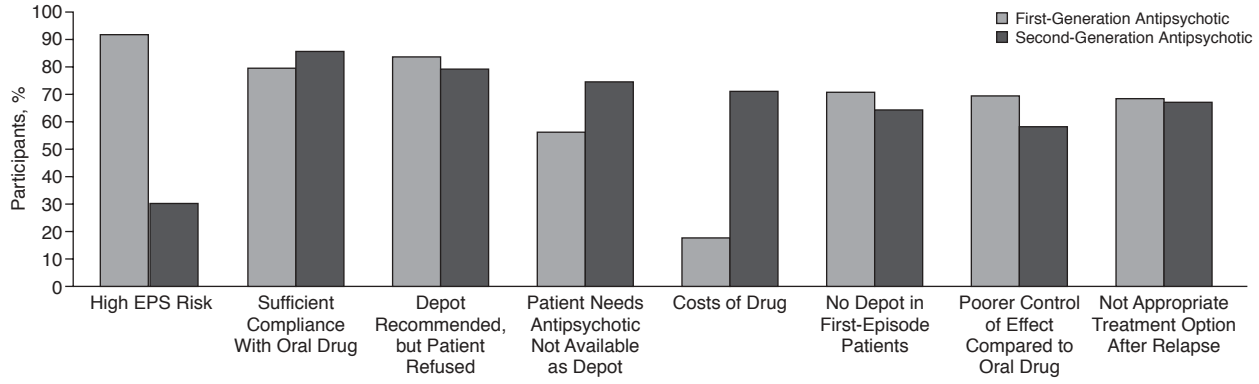
[a]Respondent Ns range from 224 to 237.
[b]Rating scale: very seldom = 1, seldom = 2, sometimes = 3, frequently = 4, very frequently = 5.
[c]Highlighted threshold of minimal mean rating score of 3 for potential impact on decision.
*$p < .001$.

a depot treatment. For this decision, we considered a minimum mean rating of "3" (i.e., this factor was at least "sometimes" taken into account) as an appropriate cutoff. Eight of 16 statements met the ≥ 3 criterion for either the FGA or SGA depot (Figure 1). For these 8 items, we then calculated how many participants scored "sometimes = 3" or higher, expressed as a percentage of the total number of all participants (Figure 2). Another 8 items scored a mean rating below "3" (Figure 1). It should be observed that ratings below "3" indicate that a given factor was predominantly seldom ("2") or very seldom ("1") taken into account, so that the influence of the respective factor should presumably be very limited.

Of the 8 factors exceeding a mean rating of "3," 5 factors were relevant (mean score ≥ 3) for both SGAs and FGAs. Thus, most of the participants indicated "sufficient compliance with oral medication" as a valid reason for not prescribing a depot formulation (FGA, 79.7%; SGA, 86.0%; see Figure 2). Furthermore, 83.3% of the psychiatrists reported that their recommendation of depot treatment with FGAs had frequently been rejected by the patients, and 79.5% reported the same statement for SGA drugs. A general attitude in the treatment of newly diagnosed patients with schizophrenia is reflected by the rule "no depot in first-episode patients," which applied as principle for a majority of the participants (FGA, 71.1%; SGA, 64.5%). Others expected a "poorer control of the antipsychotic effect" through depots compared to the oral administration of the identical drug (FGA, 69.7%; SGA, 58.3%) and viewed a long-acting injectable drug as "not an appropriate treatment option after relapse" (FGA, 68.4%; SGA, 67.5%).

Of those 8 factors militating against the decision to use depot that exceeded a mean rating of "3," a further 3 factors were considered to be relevant only for either FGAs or SGAs. Limited to first-generation drugs was the fear of "high EPS risk with depot," as this statement was chosen by 91.1% for an FGA but by only 30.6% for an SGA depot. On the other hand, the second generation lacks alternatives to the only available SGA depot drug, and consequently, 75.1% stated that the patient "needs an antipsychotic not available as depot formulation" as a reason against an SGA depot, whereas this statement applied to only 56.9% of the participants for a FGA depot. In addition, the high "costs of the depot drug" played an important role in the decision against a long-acting SGA

Figure 2. Percentage of Participants With Minimum Score of "Sometimes = 3"[a]



[a]Only statements exceeding a minimum mean rating score of 3 displayed.

formulation for 71.3% of the psychiatrists, a reason not affecting FGA depots, as only 17.8% of the respondents referred to the statement as relevant.

In all of these 8 items except for the statement "not appropriate treatment option after relapse," there was a statistically significant difference in the mean scores between FGA and SGA drugs (t test for paired samples; $p < .001$; see Figure 1).

Influence of the Type of Institution and the Age of the Psychiatrist

In accordance with previous reports,[9] we expected to find a difference in frequency of prescriptions of SGA and depot antipsychotics depending on the age of the psychiatrist and whether he or she was independently working in a private practice or employed at a clinic.

Participants aged 50 years or older offered depot treatment to statistically significantly more of their patients (42.3%, SD = 24.3%) than their younger colleagues (31.8%, SD = 20.0%; t test for unpaired samples; $p \leq .001$). They also prescribed more depot formulations (22.7%, SD = 18.1%) to their patients than psychiatrists less than 50 years of age (17.1%, SD = 11.8%; t test for unpaired samples; $p \leq .005$). On the other hand, older psychiatrists prescribed oral and depot SGAs less frequently (67.5%, SD = 27.1%) than their younger colleagues (78.6%, SD = 21.9%; t test for unpaired samples; $p \leq .001$).

Regarding frequency of depot offer or percentage of patients treated with depot formulations, there was no statistically significant difference between psychiatrists employed at a clinic and those working independently in a private practice. Still, SGAs were prescribed to a statistically significantly higher percentage of patients at clinics (79.5%, SD = 16.7%) than in private practices (71.5%, SD = 27.4%; t test for unpaired samples; $p \leq .05$). There was also a statistically significant difference in the total percentage of patients diagnosed with F20.x or F25.x (schizophrenia and schizoaffective disorder, respectively) in the 2 settings (clinic, 37.3%; SD = 19.6%; private practice, 19.3%; SD = 11.5%; t test for unpaired samples; $p < .001$).

DISCUSSION

Our survey revealed that only a minority of the participants' patients were prescribed FGA and SGA depot formulations. The main reason for not choosing an FGA depot was the fear of extrapyramidal side effects, while SGA depots were most often not prescribed because of supposed sufficient compliance with an oral SGA. In addition, the high costs of the only available SGA depot counted as reason for remaining with an oral formulation.

A further influence is the age of the treating physician. Psychiatrists aged 50 years or older offer and prescribe depot formulations more frequently but make less use of both oral and depot SGAs than do their younger colleagues. This observation may be interpreted as the effect of a change in the training programs for young psychiatrists in the last 15 years. With the introduction of the SGA drugs, depot FGA prescription rates dropped as compliance problems were thought to be tackled by the more favorable side effect profile of the modern antipsychotics. However, studies comparing compliance rates under FGA and SGA treatment showed no clinically relevant differences.[24,25] Both the frequency of offering and the prescription of depot are independent of the type of institution a psychiatrist works in, but SGAs are more frequently administered in clinics than in private practices.

Although an SGA depot has been available since 2002 and its use is recommended in expert consensus statements,[10] the participants in our survey prescribe long-

acting formulations of any antipsychotic class to only 19.5% of their patients diagnosed with schizophrenia or schizoaffective disorder. Reasons for this are partly related to the class of antipsychotic drug. Whereas FGA depots are suspected of a high EPS risk and less controllable antipsychotic effect compared to the oral formulation of a drug, SGA depots are avoided due to the high costs of the drug. As a matter of fact, cost-effectiveness of SGA depots is currently being vigorously debated and remains to be proved.[11–13] The lack of availability of SGA depot formulations for drugs such as olanzapine, quetiapine, and clozapine deters psychiatrists from prescribing a long-acting agent in the case that a patient is currently benefiting from one of these compounds. The named drugs were most frequently cited in connection with the item "patient needs an antipsychotic not available as depot formulation." While olanzapine and quetiapine basically qualify as potential depot candidates, clozapine has to be seen more critically. Considering the side effect profile, the inability to promptly stop the depot treatment may be too risky in clozapine-treated patients.

Other factors account for both antipsychotic classes and represent more general misgivings in relation to depot treatment. Most important is the participants' belief that the majority of patients are sufficiently compliant with oral antipsychotic treatment and therefore do not need or benefit from depot therapy. This factor was numerically slightly but statistically significantly more often attributed to SGAs. This finding may reflect an even stronger belief in sufficient compliance with oral treatment in this antipsychotic class compared with the first-generation drugs. Obviously, this is in contrast to numerous studies reporting compliance rates of as low as 25% with oral antipsychotics 3 months after discharge from the clinic[14] or 58% in a review of several studies on compliance with antipsychotics[15] for up to 2 years for both classes. It is also known that physicians tend to overestimate their own patients' compliance.[16] Consequently, the participants of our survey only ever offered depot treatment to 35.5% of their patients.

Furthermore, long-acting formulations of both classes are viewed as an inappropriate treatment option for first-episode patients. Again, second-generation depots are statistically significantly less affected by this reservation, although almost 65% of the participants considered the reason to be relevant (71% with FGA). This is problematic, as studies in first-episode patients have shown that the crucial predictive factor for future relapse is the discontinuation of antipsychotic treatment.[17] Moreover, even after a relapse, long-acting formulations are not considered to be a first-line treatment option for an acute episode, in spite of noted high discontinuation rates of the newly initiated therapy after discharge.[14] There was no statistically significant difference between FGA and SGA depots in regard to this item.

According to the participants, a general problem is also seen in the patient's frequent refusal of depot treatment. To our knowledge, there are not sufficient data currently available to support this statement. On the other hand, 64.5% of the participants' patients with schizophrenia or schizoaffective disorder had never been offered depot treatment, as reported in our survey, and thus their potential attitude remains completely unclear. Future research could focus on the selection criterion for patients eligible for depot treatment. Furthermore, alternatives to the common paternalistic model such as the shared decision-making technique[18] or psychoeducational programs may enhance the patient's knowledge about the different alternatives in antipsychotic relapse prevention and potential advantages of depot treatment. Moreover, basic conditions in clinics and private practices are likely not to be optimally adjusted to the needs of depot treatment. Routine administration of analgesics before injections[19] or maintaining sufficient resources for service delivery[20] may be advisable in order to facilitate depot treatment to eligible patients.

Antipsychotic depot treatment has a number of advantages, such as diminished relapse rates and reduced durations of hospitalizations, along with several other favorable aspects mentioned above.[1,2] Furthermore, depot treatment has a strong impact on compliance and is well accepted by experienced patients,[21] but this information has somehow gotten lost due to the availability of otherwise favorable oral SGA drugs. Contributing to this indecisive attitude toward depot treatment is also the fact that to date we still have no complete systematic review of all available studies comparing relapse rates under oral and depot antipsychotic treatment. A recent meta-analysis by Adams et al.[22] had to accept methodological limitations due to inclusion of short-term studies and data from inpatient follow-ups, both likely to diminish a potential advantage of depot treatment in relapse prevention. A reanalysis of the studies excluding the critical data showed the anticipated benefit of depot treatment in relapse prevention[23]; an updated review is in process.

Limitations of Our Approach

Advantages of our survey are the sample size and the anonymous acquisition of the data. Limiting factors are, first of all, the nature of a survey yielding highly subjective data that cannot be verified. No attempt was made to verify data on prescription rates or diagnosis frequency, as the focus of the survey was on the subjective attitude toward depot treatment. Secondly, psychiatrists attending an international congress on biological psychiatry may beconsidered rather progressive or open to innovations and thereby not necessarily representative of all psychiatrists. Nearly all participants were German psychiatrists, which further limits the generalizability of the results, as treatment habits and attitude toward medication vary between different countries.

CONCLUSIONS

A number of factors seem to play a role in the decision against depot treatment in schizophrenia, some in the case of both generations, some more relevant for first or second. Most reasons against depot prescription reported in our survey are not supported by the current evidence, and thus further studies are urgently needed to clarify this discrepancy.

Drug names: clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), quetiapine (Seroquel).

REFERENCES

1. Davis JM, Matalon L, Watanabe MD, et al. Depot antipsychotic drugs: place in therapy. Drugs 1994;47:741–773
2. Kane JM, Aguglia E, Altamura AC, et al. Guidelines for depot antipsychotic treatment in schizophrenia: European Neuropsychopharmacology Consensus Conference in Siena, Italy. Eur Neuropsychopharmacol 1998; 8:55–66
3. Patel MX, Nikolaou V, David AS. Psychiatrists' attitudes to maintenance medication for patients with schizophrenia. Psychol Med 2003;33:83–89
4. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry 2004;161:414–425
5. Leucht S, Wahlbeck K, Hamann J, et al. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. Lancet 2003;361:1581–1589
6. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003;60:553–564
7. Leucht S, Barnes TR, Kissling W, et al. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. Am J Psychiatry 2003;160:1209–1222
8. Hamann J, Pfeiffer H, Leucht S, et al. Are patients with schizophrenia under-treated with second-generation antipsychotics? a pilot study of the prescription practices of German psychiatrists. Pharmacopsychiatry 2003;36:309–312
9. Hamann J, Langer B, Leucht S, et al. Medical decision making in antipsychotic drug choice for schizophrenia. Am J Psychiatry 2004;161: 1301–1304
10. Kane JM, Leucht S, Carpenter D, et al. Expert Consensus Guideline Series: Optimizing Pharmacologic Treatment of Psychotic Disorders. Introduction, methods, commentary, and summary. J Clin Psychiatry 2003;64(suppl 12):5–19
11. Yang YK, Tarn YH, Wang TY, et al. Pharmacoeconomic evaluation of schizophrenia in Taiwan: model comparison of long-acting risperidone versus olanzapine versus depot haloperidol based on estimated costs. Psychiatry Clin Neurosci 2005;59:385–394
12. Llorca PM, Miadi-Fargier H, Lancon C, et al. Cost-effectiveness analysis of schizophrenic patient care settings: impact of an atypical antipsychotic under long-acting injection formulation. Encephale 2005; 31:235–246
13. Edwards NC, Rupnow MF, Pashos CL, et al. Cost-effectiveness model of long-acting risperidone in schizophrenia in the US. Pharmacoeconomics 2005;23:299–314
14. Lam Y, Velligan D, DiCocco M. Comparative assessment of antipsychotic adherence by concentration monitoring, pill count and self-report [abstract]. Schizophrenia Research 2003;60 (suppl 1):313
15. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. Psychiatr Serv 1998;49:196–201
16. Byerly M, Fischer R, Rush A. A comparison of clinician vs electronic monitoring of antipsychotic adherence in schizophrenia [poster]. Presented at the 41st annual meeting of the American College of Neuropsychopharmacology; 2002; San Juan, Puerto Rico
17. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 1999;56:241–247
18. Hamann J, Leucht S, Kissling W. Shared decision making in psychiatry. Acta Psychiatr Scand 2003;107:403–409
19. Bloch Y, Levkovitz Y, Atshuler A, et al. Use of topical application of lidocaine-prilocaine cream to reduce injection-site pain of depot antipsychotics. Psychiatr Serv 2004;55:940–941
20. Lambert T, Brennan A, Castle D, et al. Perception of depot antipsychotics by mental health professionals. J Psychiatr Pract 2003;9: 252–260
21. Walburn J, Gray R, Gournay K, et al. Systematic review of patient and nurse attitudes to depot antipsychotic medication. Br J Psychiatry 2001;179:300–307
22. Adams CE, Fenton MK, Quraishi S, et al. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. Br J Psychiatry 2001;179:290–299
23. Mentschel C. Depot-drugs may reduce relapse rates in schizophrenic outpatients: a meta-analysis. Presented at the 156th meeting of the American Psychiatric Association, San Francisco, Calif: 2003:71
24. Dolder CR, Lacro JP, Dunn LB, et al. Antipsychotic medication adherence: is there a difference between typical and atypical agents? Am J Psychiatry 2002;159:103–108
25. Valenstein M, Blow FC, Copeland LA, et al. Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors. Schizophr Bull 2004;30:255–264