Injections of Depot Antipsychotic Medications in Patients Suffering From Schizophrenia: Do They Hurt?

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Introduction: Long-acting depot injections of antipsychotic medications are an important way to monitor treatment noncompliance in patients suffering from schizophrenia. Pain and discomfort at the injection site may result in patients' refusal of depot injections. The present study is a pilot study that attempts a systematic characterization of injection site pain.

Method: Thirty-four consecutive outpatients suffering from DSM-IV–defined schizophrenia or schizoaffective disorder and treated with depot antipsychotic medications were evaluated. The pain they suffered from the injections was quantified using a visual analog scale. This evaluation was made 5 minutes before the injection, 5 minutes after, 2 days after, 10 days after, and before the next injection. Patients were also administered a modified version of the Rating of Medication Influences scale that included a specific question on the possible relationship between injection-associated pain and future compliance to depot treatment.

Results: The depot injections cause pain, which is maximal immediately after the injection, declines substantially 2 days after, and disappears by the tenth day after the injection. A correlation exists between reported injection site pain and the effect it has on patients' attitude toward the depot injection as reported by the patients. Zuclopenthixol depot injection is more painful than other depot medications.

Conclusion: Depot injections are painful. The pain they inflict has a typical course, and medication type is among the factors that influence this pain. This pain might have an effect on patients' attitude toward depot injections and thus is of importance in the management of patients suffering from schizophrenia.

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In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Drs. Bloch, Mendlovic, Strupinsky, Altshuler, Fennig, and Ratzoni have no significant commercial relationships to disclose relative to the presentation.

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Noncompliance with antipsychotic drug therapy is a major cause of relapse and resistance to therapy in patients suffering from schizophrenia.[1] The major advantage of depot antipsychotics over oral medication is facilitation and monitoring of compliance in taking medication.[1] Although there are data supporting the benefits of depot antipsychotic therapy in reducing relapse rate, we estimate that fewer than 20% of schizophrenia patients are treated in this way, with large variations between countries. This low percentage is attributed to unsupported fear of more side effects, the patients' sense of being overly controlled, and the pain or discomfort at the injection site experienced by some patients.

Despite the advantages of the depot antipsychotic preparations, few reports have addressed the issue of local pain related to their use. Reports on injection site reaction in haloperidol decanoate–treated patients have described a palpable mass and an area that became edematous, red, pruritic, and tender.[2–4] The incidences of reactions reported in the series were 2.1%,[4] 7.7%,[2] and 89%.[3] It seems that the location of the injection and the technique of injection were important factors in the appearance of injection site reactions.[2–5] These reports, however, addressed neither the severity or length of the pain inflicted by the injection, or the possible effect of injection site pain on patients' attitude toward the injection.

The present study was designed to assess the pain related to depot injections in patients suffering from schizophrenia. We examined possible factors correlated with the pain, including the patients' psychiatric condition

and the type of medication they received. We also assessed a possible relationship between the pain and the patients' attitude toward the injection.

METHOD

Subjects

Thirty-four consecutive patients were recruited into the study from a major mental health center in the center of Israel. All patients were treated on an outpatient basis. Patients were included if they were aged 16 to 65 years, had a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV criteria, and had been treated with long-acting depot medications for a period of at least 2 months. Patients were included only if there was no change in the type, dose, and interval between the last 2 injections of their long-acting depot antipsychotic injection. All patients gave informed consent to participate in the study.

Assessment and Procedures

The patients' clinical condition was evaluated by a structured psychiatric interview. Their condition was quantified with a variety of validated and frequently used assessment tools, including the Clinical Global Impressions scale (CGI),[6] the Brief Psychiatric Rating Scale (BPRS),[7] the Hamilton Rating Scale for Depression (HAM-D),[8] the Hamilton Rating Scale for Anxiety (HAM-A),[9] and the Extrapyramidal Symptom Rating Scale (ESRS).[10] The patients' weight was also evaluated. The visual analog scale (VAS) was used to quantify the pain from injections of depot medication. It is a scale commonly used in pain studies and has repeatedly been shown to reliably estimate quantitative (but not qualitative) aspects of pain.[11–13] The VAS is based on a 0-to-10 ruler. Zero represents no pain, and 10, a maximal (most imaginable) amount of pain. The patient reports the pain he or she senses on this scale.

Patients received their prescribed depot injection according to the decisions of the treating physician. All patients received their medication in the gluteus, using a 0.1-mL air lock. All injections were given by the same nurse. The dosage (mg) and volume (mL) of the injected substance were recorded for each patient. For each patient, the daily dose was calculated by dividing the depot dose by the number of days in the interval between injections.

Each patient was subjected to 5 VAS measurements at the following time intervals: 5 minutes prior to an injection, 5 minutes after the injection, 2 days after the injection, 10 days after the injection, and prior to the next injection. Since the interval between injections was different for each patient, the timing of the last measurement was also different. In addition, all patients reported on the "worst pain ever due to a depot injection" using the VAS.

Table 1. Patients' Psychiatric Scale Scores (N = 34)[a]

Score	CGI	BPRS	HAM-D	HAM-A	ESRS
Mean ± SD	4.0 ± 0.9	39.6 ± 8.5	11.2 ± 5.6	9.7 ± 5.4	6.4 ± 4.6
Range	0–5	23–57	1–24	0–19	0–16

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, ESRS = Extrapyramidal Symptom Rating Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression.

The physician examined the injection site area before the injection, a few minutes after the injection, and before the next injection for a local reaction. Rubor, edema, a palpable mass, or secretions from the area were all recorded on a scale of 0 (none) to 5 (severe).

All patients filled out a modified version of the Rating of Medication Influences (ROMI) scale,[14] including a specific question related to the patient's view on the possible relationship between injection-associated pain and future compliance to depot treatment.

Statistics

To compare and validate the results of the VAS measurements at different times and with different medications, multivariate analysis of variance (MANOVA) and post hoc comparisons using the Tukey honestly significant difference (HSD) method were used. Pearson correlation coefficients were used to examine possible correlation between the VAS results and the psychiatric rating scales. Correlation coefficients were calculated between questions related to attitude and the VAS measures.

RESULTS

The sample was composed of 25 male and 9 female patients. The patients' mean ± SD age was 39.7 ± 10.4 years (range, 23–64 years), mean length of time since first diagnosis was 15.9 ± 10.9 years (range, 1–44 years), and mean number of hospitalizations was 5.4 ± 4.7 (range, 1–21). Table 1 presents the patients' results on the HAM-D, HAM-A, ESRS, BPRS, and CGI psychiatric scales. On the basis of their CGI scores, the patients were considered by the physician as moderately ill. Their relatively high scores on the BPRS, and to a lesser degree on the HAM-D and HAM-A, reflect that, as a group, the patients suffered from active psychosis with symptoms of depression and anxiety.

Table 2 presents the number of patients receiving each of the drug injections and the mean, standard deviation, and range of the injected dose (mg), volume (mL), and daily dose. These doses are considered within the boundaries of common depot doses used to treat patients suffering from schizophrenia. Haloperidol was injected with the highest volume; a 1-way ANOVA revealed a significant difference in volume between haloperidol and all other drugs ($F = 3.86$, $df = 3,30$; $p < .05$). Post hoc comparisons using the Tukey HSD method revealed a significant differ-

Table 2. Number of Patients and Dosage, Volume, and Daily Dose of the Injected Antipsychotic Medications

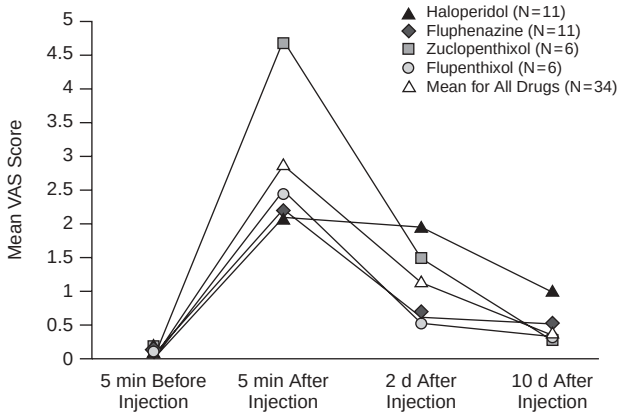
Value	Haloperidol	Fluphenazine	Zuclopenthixol	Flupenthixol
No. of patients	11	11	6	6
Injected dose, mg				
Mean (SD)	200.0 (11.8)	22.5 (13.5)	191.7 (111.4)	30.0 (16.7)
Range	50–400	6.25–50	100–400	20–60
Volume, mL				
Mean (SD)	2.0 (1.1)	0.90 (0.5)	1.0 (0.6)	1.5 (0.8)
Range	0.5–4.0	0.25–2.0	0.5–2.0	1.0–3.0
Daily dose, mg				
Mean (SD)	7.9 (4.7)	1.6 (1.2)	8.5 (4.7)	1.7 (0.6)
Range	3.6–19.0	0.4–3.6	3.6–14.3	1.4–2.9

ence in volume between haloperidol and fluphenazine ($p < .05$).

Figure 1 presents the VAS results of the patients throughout the study. As can be seen, the subjects reported a sharp increase in pain following the injection, a decline after 2 days, and a return to baseline level after 10 days. This finding was supported by a 1-way MANOVA with a repeated-measurement factor of 4 VAS measures that revealed a significant effect of measurement ($F = 24.43$, $df = 3,99$; $p < .001$) and a significant quadratic trend ($F = 49.68$, $df = 1,33$; $p < .001$). Post hoc comparisons using the Tukey HSD method revealed that VAS values were significantly higher after the injection compared with all other timepoints ($p < .01$ for all), 2 days after the injection compared with before the injection and 10 days after the injection compared with before the injection, $p < .01$ for both. The mean VAS score of the worst pain they ever had from a depot injection was 5.1, significantly higher than the VAS score immediately following the present injections (mean = 2.6) ($t = 8.65$, $df = 33$, $p < .001$). No correlation was observed between the patients' weight and the VAS measurements at any timepoint (all p values > .014).

Figure 1 also presents the VAS results of patients injected with the different drugs. As can be seen, the baseline levels of pain prior to injection were similar among the patients injected with different drugs. The patients injected with zuclopenthixol showed the sharpest increase of pain following injection. Patients injected with the other 3 drugs showed a smaller increase and did not differ from each other. In addition, while a sharp decrease of pain was seen 2 days after the injection in patients injected with fluphenazine, zuclopenthixol, and flupenthixol, patients injected with haloperidol showed only a mild decrease. No differences in pain among the drugs were present 10 days after the injection. This finding was supported by a 4 × 4 MANOVA with a main factor of drug and a repeated-measurement factor of 4 VAS measures that yielded a significant drug × VAS interaction ($F = 2.34$, $df = 9,90$; $p < .05$) and a drug × VAS interaction of the quadratic trend ($F = 2.93$, $df = 3,30$; $p < .05$). Post hoc comparisons using the Tukey HSD method performed within each VAS level revealed that significantly higher VAS values were reported 5 minutes after injection of zuclopenthixol compared with haloperidol and fluphenazine ($p < .01$ for both comparisons); no significant difference was found between zuclopenthixol and flupenthixol. No significant differences were indicated on the VAS measure 2 days after injection (all p values > .35).

Figure 1. Time Course of Pain After Depot Injection as Measured by the Visual Analog Scale (VAS)[a]



[a]The 4 groups were divided according to which depot medication the patients received and are reported separately. Standard deviation values were less than 10% of mean values.

It is important to note that the differences in the level of pain according to the VAS measures were independent of physician reports about symptomatic changes in the injection site of a wound or an inflammatory reaction.

Due to the high frequency of zero values on the VAS measures before (94%; N = 32) and 10 days after (88%; N = 30) injection, only VAS measures following injection and 2 days after were subjected for correlation analysis with the psychiatric scales. Significant Pearson correlation coefficients were observed between VAS measures 5 minutes following the injection and assessments with the HAM-D ($r = 0.41$, $df = 32$, $p < .05$), HAM-A ($r = 0.37$, $df = 32$, $p < .05$), and BPRS ($r = 0.36$, $df = 32$, $p < .05$), but not with the CGI or the ESRS. No significant correlation was observed between VAS measures 2 days after injection and scores on any of the psychiatric scales (all r values < 0.25, p> .14).

Correlation coefficients were calculated between the patients' reports of the effects of injection pain on attitude toward injections of antipsychotic medications and the VAS measures 5 minutes and 2 days after the injection. A significant correlation was observed between the reports and the VAS measures 2 days after the injection ($r = 0.51$, $df = 32$, $p < .01$), and a marginally significant correlation was observed between the reports and the VAS measures 5 minutes following the injection ($r = 0.33$, $df = 32$, $p = .06$).

DISCUSSION

Our results support the "common sense" view that the long-acting depot injections hurt. Our study typifies the pattern of this pain. The pain is maximal immediately after the injection, declines 2 days after, and disappears by the tenth day after the injection. This time course, as well as the lack of objective findings in the injection site, distinguishes the pain we report from the time course described with injection site reaction, in which the maximal pain usually appears days after the injection.[2–4] The finding that the maximal intensity appears immediately after the injection supports the view that an immediate reliever, such as a local anesthetic, can ease this pain. It can be assumed that questioning about pain, especially before the injection, can alter the subjective experience of the magnitude of the pain. While this is a possibility that would bias toward overestimation of the pain (as in any study that examines a subjective finding), the fact that the pain from these injections was not considered by most of the patients to be the maximal pain they ever experienced from an injection argues for the robustness of these pain findings.

We have found injection site pain to be influenced by several factors. According to our findings, zuclopenthixol depot injection is significantly more painful than the other depot injections used in our study, despite the small number of patients in the zuclopenthixol group (N = 6). Is this difference related to the medication itself or to the vehicle? (The depot antipsychotics are injected using a vehicle that gives them their depot characteristic.) Zuclopenthixol and flupenthixol use Viscoleo as a vehicle, whereas fluphenazine and haloperidol use sesame oil as a vehicle. The fact that the difference between the pain inflicted by flupenthixol and zuclopenthixol did not reach significance supports the possibility that it is the vehicle that inflicts the pain. On the other hand, it is possible that, due to the relatively smaller size of the flupenthixol group compared with the haloperidol and fluphenazine groups, the difference did not reach significance. It is important to note that since flupenthixol and zuclopenthixol are prepared with a similar vehicle, the fact that flupenthixol did not differ from fluphenazine and haloperidol shows that the substance, rather than the vehicle, causes the pain. While the question of whether the medication or the vehicle inflicts the pain might have importance for developers in the pharmaceutical industry, for the practicing physician, our results are useful because they indicate that zuclopenthixol depot is more painful than haloperidol depot or fluphenazine depot. Other variables that could cause this effect, including the volume of the injection or the relative daily dose of zuclopenthixol, were not different from the other medications.

Another finding is that only patients who received haloperidol tended to experience pain 2 days after the injection. This effect is difficult to interpret. On the one hand, fluphenazine is given with the same vehicle as haloperidol (sesame oil), but no persisting pain was reported by subjects using fluphenazine; on the other hand, haloperidol was given in larger volumes compared with fluphenazine. Thus, the results could not permit a firm conclusion about whether the cause of continuing pain is the medication itself, the vehicle, or the larger volume of injection.

In our study, anxiety and depression (as measured by the HAM-D and HAM-A) were correlated with the severity of pain. Similar findings were reported in other studies with nonschizophrenic patients.[15–17] The interactions between an affective burden and the processing of the perception of pain are probably related to both physiologic and psychological factors.

Does the pain inflicted by antipsychotic medications have clinical significance? Some earlier reports based on case reports indicate a relative insensitivity to pain among patients suffering from schizophrenia.[18] When objective evaluations were used, the difference in pain sensitivity between patients and controls seems to be more closely related to attitude than to biological factors.[19] In the present study, the patients complained of pain. Our finding that the patients correlate the severity of the pain with their attitude toward the injections may suggest that depot-associated pain influences patients' attitude toward depot injection treatment. Additional, long-term prospective studies should be conducted to substantiate this hypothesis and examine if this attitude influences compliance.

Using an injection to overcome problems of compliance and monitoring has an important impact on the patient's sense of autonomy and trust, patient-doctor relations, and probably the straightforward unease produced by exposure of certain body parts. Bearing the impact of these factors in mind, it would seem that attitudinal issues play a major role in the use of depot antipsychotic medications. This point is highlighted by the wide variety in the use of depot antipsychotic injections between countries and between centers. The attitude of therapists and doctors as well as that of other staff members probably has an impact on the attitude of the patient toward the injection and perhaps even on the pain reported. In this study, such issues were dealt with partly by having all patients in the study group receive the injections by the same nurse and in the same setting. But the emotional issues were not addressed specifically and definitely deserve more research. Still, these attitude- and emotion-related factors cannot explain such findings as the difference in the reported pain between the different medications. It seems that our results support the existence and probable importance of the pain caused by depot injections of antipsychotic medications.

To conclude, the present study indicates that depot antipsychotic injections cause pain in patients suffering

from schizophrenia. The severity of this pain is correlated with the type of medication used and the patient's condition. This pain may influence attitude toward depot antipsychotic treatment and thus may be of significant clinical importance.

Drug name: haloperidol (Haldol and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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Note: For the CME Posttest for this article, see pages 916–917.