

Medical Press
Pre-Launch Feature Outline
Distribution: Top 10 Markets

Suggested titles

“Filling the droperidol gap.”

“Developments in the field of acute phase schizophrenia management.”

“Droperidol voluntarily withdrawn – what is the future for treatment of acute phase schizophrenia?”

Rationale/ Aims

- Prepare the market for the launch of intramuscular olanzapine.
- Create a need for intramuscular olanzapine through the promotion of awareness of safety issues surrounding current typical IM treatments for acute agitation associated with schizophrenia.
- Build awareness of the need for atypical intramuscular management of acute phase.
- Highlight the strengths of atypical antipsychotics.
- Discuss potential future intramuscular launches of atypical antipsychotics.

Please note that where the IM formulation is being submitted for approval for acute agitation in schizophrenia, bipolar disorder and dementia, the objectives and focus of the feature should be adapted to reflect this, rather than focusing solely on acute schizophrenia.

Target Media

- Emergency psychiatrist publications.
- General psychiatrist publications.
- General medical press.
- Psychiatric nursing press.
- Hospital pharmacist press (not community pharmacy press).

For scientific journals, this outline should be cut down and submitted as an editorial.

News Hook

The recent voluntary withdrawal of droperidol in intramuscular formulation in Belgium, the Netherlands and the United Kingdom, due to concerns over its QTc safety, * has raised the issue of safety and suitability of current treatment options for the management of acute phase schizophrenia. The withdrawal of droperidol could yet extend to other countries.

With the withdrawal of this frequently prescribed compound, is there a gap in the treatment options available to the acute care team? What new treatments may soon be available to take the place of older, less effective compounds?

Timing

1-2 months prior to launch of intramuscular olanzapine.

Length of feature article: 1000-1500 words

Process

Writing the feature article

- Consider the content carefully - never make it seem that olanzapine already has a license for intramuscular use (although it is acceptable to allude to the fact that this may be a future outcome). One way to do this is to avoid definitive language.
- Make it clear in notes to the editor, or within the article, that olanzapine does not hold an intramuscular license to date.
- Use the generic name, not the brand name.
- The outline may be used when briefing a freelance writer. A third party spokesperson/authoring Key Opinion Leader (KOL) should also be identified to the freelance writer in conjunction with such discussions.

Authoring of the feature article

- Utilise a local KOL to author the feature, either by drafting the full feature for KOL review or by giving the outline to a KOL to develop the feature.
- The KOL has full editorial control over the feature; if they wish to make changes, this should be encouraged and accommodated.
- The KOL could be:
 - An investigator in an olanzapine intramuscular trial.
 - Lilly-friendly key opinion leader, who has previously been involved in other areas of olanzapine.
 - A participant of a Lilly advisory board.
- KOLs can be paid honorarium for their time/input in reviewing/authoring of the article. It should be made clear that this payment is for their time and not to sway the content of the article. If using a member of a relevant advisory board, KOL authoring could be covered by a retainer given for participation in advising the board. This is the best option to use, if possible.

When placing the feature

- Any feature on a non-approved indication should be submitted to medical media only, not consumer media.
- The feature should be submitted to the publication by the authoring KOL.

Additional uses

- Background information for advocacy groups.
- Basis for discussion with key customers (i.e. psychiatrists/ emergency psychiatrists).
- Background information for media pack at time of launch (approval).
- Internal training purposes.
- Local journalist briefing on acute phase of schizophrenia presented by KOL.

Content

Background

Droperidol, one of the most frequently prescribed intramuscular antipsychotics for the treatment of acute phase schizophrenia, was voluntarily withdrawn in Belgium and the UK effective from March 31 due to concerns over its QTc safety. It was also recently withdrawn in the Netherlands. This withdrawal may also extend to other countries.

How will the gap droperidol has left be filled? What different types of new drugs are in development that may help fill the gap?

Message Flow

- It is vital for the patient, the physician and the emergency care team that the acute phase of schizophrenia is managed rapidly, safely and effectively and that management can be sustained in the maintenance phase.
↓
- The emergency care team needs a wide range of treatment options available for the tailoring of the most appropriate treatment for patients in the acute phase.
↓
- Currently available intramuscular typical treatments for acute agitation in schizophrenia are associated with serious side effects, including acute dystonia*, significant prolongation of QTc interval and excessive drowsiness. This can be exacerbated by the co-administration of benzodiazepines, which are needed to provide additional and rapid sedation.
↓
- Due to the current lack of IM formulation atypical antipsychotics available throughout Europe, physicians who treat acutely agitated patients have only one choice – older typical IM antipsychotic drugs - despite the fact that it is increasingly accepted that atypical antipsychotic drugs have a superior efficacy and favorable safety profile.^{1,2,3,4}
↓
- Once the acute situation has been managed, the patient is then initiated into a stable longer-term maintenance regimen. The lack of atypical options in intramuscular formulation has meant that psychiatrists must make a choice: whether to continue maintenance therapy with a typical antipsychotic drug in the knowledge that an atypical antipsychotic may provide superior efficacy and a more favorable safety profile; or to switch the patient to an atypical antipsychotic drug for maintenance therapy, and risk symptom breakthrough and/or relapse during the switching process.
↓
- It is anticipated that, this year, atypical antipsychotics will become available for the first time in IM formulation for the treatment of acute agitation associated with schizophrenia. This represents a potential breakthrough for the patient and emergency care team.

“Filling the droperidol gap.”

Introduction

Droperidol has recently been withdrawn in Belgium, the Netherlands and the UK, and it is possible that this may happen in other countries. What therapies are available to fill the gap? Lorazepam, a benzodiazepine, is currently discussed as a potential alternative. However, more advanced IM treatments may soon be available to provide a superior alternative to lorazepam, droperidol and other typical antipsychotics options such as haloperidol. This article examines how the acute phase of schizophrenia is currently managed and what future treatments may have a role in replacing droperidol.

Patients suffering from an acute episode of schizophrenia often present with acute agitation. The range of symptoms include, tension, hostility, uncooperativeness and excitement that can be severely distressing to the patient, carers and healthcare providers. Patients may also experience 'positive symptoms', which include delusions and hallucinations.

These symptoms can lead to a failure for patients to appreciate they are ill, often resulting in refusal to take their medication.

The acute phase of schizophrenia can be seen as a “blueprint” for the future management and treatment of the condition. Patients’ first experience of how their illness is managed in the acute stage influences their future perceptions about treatment and can affect long-term compliance and their relationship with the care team.

Symptoms of Acute Schizophrenia

- Acute agitation
 - Hostility and/or violence
 - Delusions
 - Hallucinations
 - Paranoia
- } Positive Symptoms

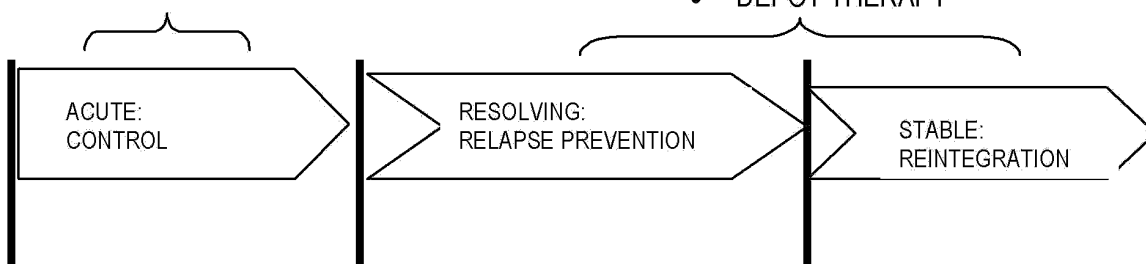
Stages of Schizophrenia

It is helpful to clinicians to consider three stages of schizophrenia each requiring particular treatment approaches and therapeutic goals:

- The **acute phase**, lasting for about 4-6 weeks, during which patients display active and extreme symptoms of schizophrenia – the goal in this phase is to rapidly control the symptoms.
- The **resolving phase**, lasting for about 4-6 months, when patients have generally recovered from active symptoms but are susceptible to relapse and the therapeutic goal is to prevent this from happening.
- The **stable phase**, which lasts for as long as the patient is in remission – again, the goal is to prevent relapse but also to treat the other longer term symptoms associated with schizophrenia that may predominate during this phase, and to ultimately facilitate reintegration.

- ORODISPERSIBLE THERAPY
- IM THERAPY

- ORAL THERAPY
- ORODISPERSIBLE THERAPY
- DEPOT THERAPY



→ 4-6 WEEKS → → 4-6 MONTHS → → 6 MONTHS + →

Current Therapy

Current treatment options depend on the administration of IM typical antipsychotic drugs, often co-administered with benzodiazepines, which are used to accelerate tranquillisation. The use of benzodiazepines, however, can result in excessive sedation and risk of respiratory depression.

The most widely used IM antipsychotic drugs are haloperidol, zuclopenthixol and droperidol (now withdrawn). [INSERT APPROPRIATE DRUGS] These are effective in the alleviation of acute agitation. However a number of typicals are associated with significant side effects, the most serious of which are acute dystonia, clinically significant QTc interval prolongation, extra pyramidal symptoms (EPS) and excessive sedation.

It is increasingly accepted that atypical antipsychotics generally have a superior efficacy and favorable safety profile compared to conventional antipsychotics. . World Psychiatric Association (WPA) interim guidelines recommend widespread access to atypical antipsychotics. However, atypical antipsychotics have not been available throughout Europe in IM formulation, leaving physicians only one choice in the acute phase of schizophrenia – to treat with intramuscular typicals. The withdrawal of droperidol limits the choices available to the emergency care team still further.

Future developments

It is anticipated that, this year, atypical antipsychotics will become available for the first time in IM formulation for the rapid treatment of acute agitation in schizophrenia.

Atypical antipsychotics promise to offer a range of benefits to the acute care team – rapid, effective and sustained relief of agitation and positive symptoms without EPS and other side-effects. Atypicals also allow simplification of transition from initial IM therapy to subsequent maintenance oral therapy.

Two intramuscular atypical antipsychotics are anticipated to become available this year; Zyprexa (olanzapine) is approved in the US, and has received a positive CPMP opinion in Europe, and ziprasidone, which is not currently approved in either region.

Both drugs in intramuscular formulation recently came before the U.S. Food and Drug Administration's Psychopharmacologic Drugs Advisory Committee. The committee recommended approval of intramuscular olanzapine for the control of agitation associated with dementia, schizophrenia and bipolar mania. The committee voted unanimously to recommend approval of intramuscular olanzapine based on its safety and efficacy presented in the clinical trials and the FDA issued an approvable letter for IM olanzapine. Intramuscular olanzapine recently received full approval in the US. The approval of the intramuscular formulation of ziprasidone is pending.

Intramuscular olanzapine was recently recommended for approval for the rapid control of agitation in patients with schizophrenia by the European Agency for Evaluation of Medicinal Product's (EMA) Committee for Proprietary Medicinal Products (CPMP).

Intramuscular olanzapine can build upon a proven track record in terms of efficacy and safety in oral formulation and may present a recognisable and trusted compound in intramuscular formulation.

Initial clinical trials comparing atypical intramuscular compounds with typicals are encouraging; in a study of 311 patients with schizophrenia, 10mg IM olanzapine showed superiority over 7.5mg IM haloperidol in reducing acute agitation in 15 minutes after injection with IM haloperidol only achieving this one hour after injection. A reduction in agitation was seen with olanzapine at two hours and at 24 hours and was significant versus placebo. Statistically fewer patients experienced EPS symptoms during treatment with intramuscular olanzapine compared to intramuscular haloperidol. Importantly, in addition to IM olanzapine being as efficacious as IM haloperidol, there were no episodes of acute dystonia (severe and frightening muscle spasms that cause painful twists of the body) while 6.6% of patients who received the typical IM formulation experienced dystonic events.^{5, 6} The incidence of prolonged QTc interval during treatment with olanzapine was similar to placebo.

For more compliant patients, oral treatment with olanzapine has also been proven beneficial in the treatment of the acute phase. In a large multi-centre study involving 1,996 patients, patients treated with oral olanzapine showed a significantly greater improvement in behavioural agitation when compared with patients treated with oral haloperidol. Whilst both groups showed greater similar reductions in agitation scores during the first three weeks of therapy, olanzapine-treated patients demonstrated a significantly greater improvement at weeks 4, 5 and 6.⁷

Oral olanzapine is currently indicated for the treatment of schizophrenia, and in the US for the short-term treatment of acute manic episodes associated with bipolar disorder. It has been used in more than 6 million patients since its launch in 1996.

Conclusion

The ultimate goal of schizophrenia treatment is re-integration of the patient into society. The acute phase of schizophrenia needs to be effectively managed in order to gain the trust of the patient, to comply with long-term treatment, and to achieve reintegration.

The withdrawal of droperidol leaves a gap in the range of options available in the treatment of the acute phase. This is of particular concern, as the acute care team needs a range of flexible, rapid-acting, and effective treatments available to treat all phases of the emergency situation.

The anticipated forthcoming availability of atypical antipsychotics in an IM formulation could be a major step forward in the treatment of acute agitation associated with schizophrenia, introducing patients to the benefits of atypicals when they need it most.

References

- ¹ Kennedy E, Song F, et al. Risperidone versus typical antipsychotic medication for schizophrenia (Cochrane Review), In: The Cochrane Library, Issue 4, 2000.
- ² Wahlbeck K, Chiene M et al. Clozapine versus typical neuroleptic medication for schizophrenia (Cochrane Review), In: The Cochrane Library, Issue 4, 2000.
- ³ Quraishi S et al. Depot flupenthixol decanoate for schizophrenia or other similar psychotic disorders (Cochrane Review), In: The Cochrane Library, Issue 4, 2000.
- ⁴ Thornley B et al Clorpromazine versus placebo for schizophrenia (Cochrane Review), In: The Cochrane Library, Issue 4, 2000.
- ⁵ Wright P et al. A double-blind dose response study comparing intramuscular olanzapine, haloperidol and placebo in acutely agitated schizophrenic patients. *European Neuropsychopharmacology*.2000;10:S304
- ⁶ Wright P et al. A double-blind study of intramuscular olanzapine, haloperidol and placebo in acutely agitated schizophrenic patients. *European Neuropsychopharmacology*.2000;10:S304
- ⁸ Kinon et al 'Effective resolution of acute presentation of behavioural agitation and positive psychotic symptoms in schizophrenia with olanzapine' presented 9-13 September 2000 at the 13th European College of Neuropsychopharmacology Congress.

Notes to editors:

* What is QTc prolongation?

The QT interval on an electrocardiogram (ECG) reflects the length of time it takes the electrical system in the heart to repolarise after each beat. The rate corrected QT interval (QTc) is adjusted for heart rate. A significantly prolonged QT interval on the ECG (>500 milliseconds) has been associated with life-threatening arrhythmias and sudden death.

*What is acute dystonia?

A severe side effect associated with typical antipsychotics, acute dystonia is a movement disorder in which painful contractions of the muscles of the head and neck occur and breathing and swallowing may become difficult.