The management of first episode affective psychosis: efficacy and current guidelines

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Advisory Boards: Endo; Janssen; Lundbeck; Roche
SIGN 127
Management of perinatal mood disorders
A national clinical guideline March 2012

“…treatments would typically involve one or more drugs from the antidepressant, mood stabilising or neuroleptic groups and/or ECT.”

The NICE APMH guideline recommends the use of medication which would normally be used in the management of bipolar disorder, schizoaffective disorder or schizophrenia, prioritising treatments which have less evidence of adverse effects in breast feeding.

Postpartum psychosis should be managed in the same way as psychotic disorders at any other time, but with the additional considerations regarding medication use during breast feeding.
Maudsley Guidelines
11th ed. Taylor D, Paton C, Kapur S

1st episode psychosis algorithm

- Use SGA or patient / carer choice
- Titrate to minimum effective dose
- Wait 2-3 weeks
- Not effective, switch to other SGA or FGA
- Not effective, use Clozapine

NB if in clinical equipoise, use olanzapine
NICE clinical guideline 82

Schizophrenia Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care

- 1st episode treatment: “..offer oral antipsychotic medication” after d/w patient & weigh relative SE profile
- “..should be considered an explicit individual trial” at optimum dose for 4-6 weeks
- Don’t use loading doses, or combination antipsychotics
- Consider ECG if in SPC
Effectiveness studies in 1st episode psychosis

- EUFEST (2008) - no significant difference but olanzapine lower discontinuation rate
- CAFÉ (2007) – no difference between quetiapine; olanzapine; risperidone
- TEOSS (2010) – 8-19yo; only 12% continue over a year. No difference between risp; olanz; molindone

*Examining the effectiveness of antipsychotic medication in first episode psychosis*  
The risk of rehospitalisation associated with the initiated antipsychotic compared to haloperidol

Vertical bars indicate 95% confidence intervals

Tiihonen et al BMJ July 2006; 333:224
Nascent SIGN schizophrenia guideline...near you Q1, 2013

• Evidence based (not consensus)
• MDT + patients / carers
• Started 2010
• Focussed on RCT evidence emerging after NICE CG82
• External peer review
Good practice point – perinatal

Roch Cantwell

Clinicians should be aware that women with schizophrenia have an increased risk of relapse in the postpartum period.

Relapse risk is increased further if they are unwell in pregnancy.
Insufficient evidence .... on interventions to reduce risk of relapse specific to the perinatal context
Good practice point

Consider joint admission of mother and baby where a woman with schizophrenia experiences a postpartum relapse.
Antipsychotic drugs & fetal and infant outcomes?

- No conclusive evidence for structural teratogenicity
- Association between FGAs in pregnancy & low birth weight
- Association between SGAs and increased birth weight
- Association between clozapine /olanzapine and gestational diabetes mellitus
Recommendation (level 3 evidence)

Women taking antipsychotics during pregnancy should be monitored for alterations in fetal growth. Additional monitoring for blood glucose abnormalities is required where olanzapine or clozapine are prescribed.
Pharmacotherapy in 1st episode

• Sameer Jauhar & Mark Taylor
Discontinuation slightly favouring SGAs over Haloperidol

(EUFEST, Lancet, 2008)

Small difference in symptom scores, not clinically relevant

(Crossley, BJP, 2009)
Fig. 5 Extrapyramidal side-effects in both groups using standardised mean differences.

A highly significant difference favouring atypicals was found (p < 0.001). Note that all individual trials favour atypicals. Heterogeneity: $I^2 = 12.4$ (df = 8), $p = 0.16$, $I^2 = 38%$. EPN: Early Psychosis Global Network, GRNS: German Research Network on Schizophrenia, EUPHEST, European First-Episode Schizophrenia Trial.

Fig. 4 Comparison of weight gain between the two groups.

Data expressed in kilograms, and pooled using random effects model. Significant weight gain found in atypicals group (p = 0.001, $I^2 = 79.9%$, EPNG: Early Psychosis Global Network, GRNS: German Research Network on Schizophrenia, EUPHEST: European First-Episode Schizophrenia Trial.)
Findings

- No significant difference between individual medications in efficacy or discontinuation rates
- *Differing side-effect profiles*
Treatment strategy –  
- assessing response

• No systematic evidence
• Consensus guidelines:
  For at least two weeks, with four week review
  If poor response, consider other factors
    (substance misuse, adherence)
  If no response, consider change
  If partial response, reassess at 8 weeks
Predicting response

- Observational search

- Better response:
  - Early antipsychotic response
  - Female gender
  - Better pre-morbid social function

- Poorer response:
  - Male gender
  - Substance misuse, forensic history, decreased insight
Dose

- One trial from NICE (2009)
  - Schooler, (AJP, 2005)
  - Risp 3.3mg, Hal 2.9mg → remission in 75%

- Cochrane review of Risperidone
  - 4 trials, two with dose<2mg
  - <2mg, increased discontinuation due to lack of efficacy
Duration of antipsychotic use?

Only one RCT revealed by systematic search

**Fig 2** Kaplan-Meier analysis in remitted first episode psychosis patients with and without antipsychotic maintenance treatment. Median duration of follow-up was 145 (interquartile range 41-351) days for quetiapine group and 106 (57-243) days for placebo group.
Management of Weight Gain

• Review level evidence has shown that a variety of non-pharmacological approaches were effective in reducing weight compared to treatment as usual. Also consider SIGN 115 on management of obesity.

• Review level evidence on the use of metformin (off label use) in antipsychotic weight gain. Possible benefits were confounded by co-administered weight and lifestyle intervention programmes.
Acute treatment of schizophrenia – what is the evidence?

Karen Fraser & Mark Taylor

(2) Post NICE systematic reviews and meta-analyses identified that helped to inform the key question:

Leucht, S, Corves, C, Arbter, D, Engel, RR, Li, C and Davis, JM.
Second-generation versus first-generation antipsychotic drugs for schizophrenia: A meta-analysis (Lancet: 2009 373 31-41)

150 studies

Four second generation drugs, amisulpride, clozapine, olanzapine and risperidone were more efficacious for the treatment of overall schizophrenia symptoms than first generation drugs.

Leucht et al. Lancet 2009; 373 : 31-41
Acute Treatment: Outcomes form Post-NICE evidence

• Amisulpride, olanzapine, risperidone and clozapine had superior efficacy when compared with FGAs in terms of overall efficacy, with small to medium effect size.

• Other SGAs were NOT more efficacious than FGAs.

• Head-to-head comparison of SGAs showed small but inconsistent differences with respect to efficacy, balanced by potentially large differences in adverse effect profiles for individual patients – this was consistent with findings from the SGA Cochrane reviews.
In patients with an acute exacerbation or recurrence of schizophrenia olanzapine, risperidone or amisulpride should be offered as first choice antipsychotic.

Consideration should be given to previous response to individual antipsychotic medications and relative adverse effect profiles.

Grade of recommendation: A
Acute treatment of schizophrenia – dose & duration?

(3) BAP Guideline – consensus guideline (Barnes et al 2011)

• Initial minimum period of 4 weeks before altering treatment, taking into account any emergent adverse effects

• No evidence that exceeding licensed doses has additional benefit and that optimal dose for most antipsychotics is below the recommended maximum
PREDICTING RELAPSE

Steve Lawrie & Fiona Lang

- Relapse risk is especially increased if medication is stopped abruptly, but ~ half of patients will relapse within six months even if medication is withdrawn gradually. Other predictors of relapse included persistent symptoms, poor adherence, lack of insight and substance misuse. [Evidence level 1++]

- A Cochrane review (Almerie 2007, n=1,042), found that those stopping chlorpromazine had a 6.8 fold increase in risk of relapse in the short term (up to 8 weeks), and of 4.0 times in the medium term (nine weeks to six months) compared with patients who continued medication. [Evidence level 1++]

- Leucht et al (2012) – At one year relapse rate = 27% drugs & 64% placebo (RR= 0.4). Depot (RR 0.31) better than orals (RR 0.46). No predictors of risk
Recommendations
Relapse prevention

• Grade A - Schizophrenia in remission should be offered maintenance antipsychotic drugs. Usually the drug that was used during their last acute episode, assuming efficacy and tolerability.

• Grade B - For maintenance treatment prescribers should consider amisulpride, olanzapine or risperidone as the preferred medications with chlorpromazine and other low potency first generation antipsychotics providing suitable alternatives.
Dose - Recommendation

• Grade B - Patients with schizophrenia which is in remission should be offered maintenance treatment with antipsychotic drugs at low to moderate regular dosing of around 300-400 mg of chlorpromazine, 4-6 mg of risperidone, or their equivalents daily.
Duration of treatment Recommendation

• Grade A - Patients with schizophrenia which is in remission should be offered maintenance treatment with antipsychotic drugs for (a minimum of) two years.
Depots / LAIs
Recommendation

• Grade B - Patients with schizophrenia which is in remission who request depot and those with medication adherence difficulties should be offered maintenance treatment with depot zuclopenthixol decanoate.

• GPP - Patients who have responded to oral risperidone and want to receive depot should be offered paliperidone or risperidone long-acting injection. This can also be offered to those who prefer deltoid injections.

• GPP - Patients should be given the option of oral or depot medication, in line with their preference.
Treatment resistant schizophrenia
Mark Taylor & Fiona Lang

- Q: Which is the most effective antipsychotic?
- A: Clozapine – should be tried once adequate trial of SGA has failed (A) (NICE + 2 big meta-analyses)

- Q: If only partial response to clozapine, then what?
- A: Augment with another SGA (A) or lamotrigine (B) for >= 10 weeks (NICE + 2 meta-analyses; one meta-analysis)
Treatment resistant schizophrenia

- Q: Switching antipsychotic (due to lack of or partial response)?
  - A: Not promising….but choose antipsychotic with different receptor binding profile (5 RCTs)

- Q: High dose antipsychotic any good in treatment resistance?
  - A: No convincing evidence – last resort

- Q: ECT any use in treatment resistance?
  - A: Only as last resort in combo with an antipsychotic (10 RCTs, n=392)
Monitoring for adverse effects …but done in 1ry or 2ndy care?

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>3 months</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of physical illness</td>
<td>√</td>
<td></td>
<td>√</td>
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<tr>
<td>Smoking history</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>BMI or waist circum or weight</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>BP</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>HbA1C or random glucose</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Random lipids</td>
<td>√</td>
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Prolactin and / or ECG as clinically indicated
Glasgow Antipsychotic Side effect Scale - rationale

- Regular systematic review desirable
- Life in a busy OPC or WR
- “What’s a chillblain?”
- Vehicle that enhances discussion & disclosure
## Existing side-effect rating scales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Number questions</th>
<th>Completion</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson Angus Scale (SAS) (Simpson and Angus, 1970)</td>
<td>10</td>
<td>Clinician rated</td>
<td>Objective rating of EPSE, quick and easy to perform</td>
<td>Focus on extrapyramidal side effects (EPSE) only</td>
</tr>
<tr>
<td>Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976)</td>
<td>12</td>
<td>Clinician rated</td>
<td>Objectively records presence and severity of involuntary movements; quick to perform</td>
<td>Focus on abnormal movements only</td>
</tr>
<tr>
<td>Extrapyramidal Side Effect Rating Scale (ESRS) (Chouinard, et al., 1980)</td>
<td>12</td>
<td>Clinician rated</td>
<td>Quick to perform, objective documenting of EPSE</td>
<td>EPSE only. No differentiation between dyskinesia and dystonia</td>
</tr>
<tr>
<td>Drug Attitude Inventory (Hogan, et al., 1983)</td>
<td>30</td>
<td>Self rated</td>
<td>Simple to understand questions and true/false answers. Assesses attitude</td>
<td>Not specifically aimed at detecting antipsychotic side-effects</td>
</tr>
<tr>
<td>Side Effects Rating Scale for the Registration of Unwanted Effects of Psychotropics (Lingjaerde, et al., 1987)</td>
<td>47</td>
<td>Clinician rated</td>
<td>Covers an extensive range of side effects from antipsychotic medication</td>
<td>Requires a lengthy semi structured interview and clinical observation</td>
</tr>
<tr>
<td>Barnes Akathisia Rating Scale (Barnes, 1989)</td>
<td>4</td>
<td>Clinician and self rated components</td>
<td>Both subjective and objective rating of akathisia; quick</td>
<td>Focuses on akathisia only</td>
</tr>
<tr>
<td>Hillside Akathisia Scale (HAS) (Fleischhaker, et al., 1989)</td>
<td>5</td>
<td>Clinician and self rated components</td>
<td>Both subjective and objective rating of akathisia; quick</td>
<td>Focuses on akathisia only</td>
</tr>
<tr>
<td>Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) (Day, et al., 1995)</td>
<td>51</td>
<td>Self rated</td>
<td>Assesses wide range of side effects; red herring questions for over-reporting of side-effects</td>
<td>One-word symptoms that can be difficult to understand</td>
</tr>
<tr>
<td>Antipsychotic Non-Neurological Side Effect Rating Scale (ANNERS) (Yusufi, et al., 2005)</td>
<td>35</td>
<td>Clinician and self rated components</td>
<td>Covers wide range of side effects for 1st and 2nd generation antipsychotics</td>
<td>Lengthy and time consuming</td>
</tr>
</tbody>
</table>

*From: Waddell & Taylor, J Psychopharmacol 2008. With approval*
Glasgow Antipsychotic Side effect Scale - Method

- Literature review
- Physician & patient focus group hierarchy rating
- One page format; self report; plain English; categorical severity; frequency & distress rated
- 3 CMHTs, 50 patients, all Δ, on antipsychotic(s)
- All do GASS & LUNSERS, then GASS in 1 week
- 50 normal comparisons do GASS
- Validity & reliability
Mean ages and GASS scores of participants

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Cases (n = 50)</th>
<th>Comparisons (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) [SD]</td>
<td>41.4 [9.1]</td>
<td>39.9 [14.1]</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>24–65</td>
<td>19–65</td>
</tr>
<tr>
<td>No. males</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Mean GASS [SD]</td>
<td>14.3 [10.5]</td>
<td>3.6 [4.1]</td>
</tr>
</tbody>
</table>

GASS, Glasgow Antipsychotic Side-effect Scale; SD, standard deviation.

From: Waddell & Taylor, J Psychopharmacol 2008. With approval
Severity categories for GASS

From: Waddell & Taylor, J Psychopharmacol 2008. With approval
"Mr. Osborne, may I be excused? My brain is full."