Northern Treatment Advisory Group

Aripiprazole prolonged-release injection for schizophrenia

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Summary

- Aripiprazole is an atypical antipsychotic drug used in the treatment of schizophrenia which has been available in oral and short-acting injectable formulations for some time. A long-acting injectable (LAI) depot formulation (Abilify Maintena®, Otsuka Pharmaceuticals) was recently launched in the UK, and is licensed for the maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

- A pivotal phase III trial (n=662) found that aripirazole LAI was non-inferior to oral aripiprazole for the primary outcome of impending relapse after 26 weeks treatment. A second trial showed that it was superior to placebo.

- Pooled safety data published by the EMA did not identify any new safety concerns associated with the aripiprazole depot compared to existing formulations, other than injection site pain. The incidence of extrapyramidal symptoms was higher than with oral aripiprazole (18.4% vs. 11.7%), and a post-authorisation study has been requested to investigate. Clinically-significant weight gain was comparable between the depot and oral formulations, but weight loss was more common with the depot.

- Three other atypical antipsychotics are currently available in depot form: olanzapine, risperidone and paliperidone. The licensed populations for the four depots do not substantially overlap, due to differing requirements for patients to be stable on oral medicines.

- Aripiprazole is less costly than the other available depots, with the exception of the lowest dose of risperidone. None of the available depots can be self-administered, and administration costs will vary with setting. Aripiprazole is administered monthly, as is paliperidone. Administration costs will be lower for these than preparations which must be administered 2-weekly (risperidone, some olanzapine doses). The difference in licensed populations makes further cost analysis inappropriate.

- Depot antipsychotics may reduce the risk of relapse in schizophrenia compared to oral drugs. However some patients may find depots disempowering, and prefer a regimen over which they have more control.

Introduction and background

Schizophrenia is a major psychiatric disorder in which an individual's perception, thoughts, mood and behaviour are significantly altered. The symptoms of schizophrenia are often differentiated between positive symptoms, including hallucinations, delusions, and behavioural disturbances, and negative symptoms such as emotional apathy, social withdrawal and self-neglect. Each individual will have a unique combination of symptoms and experiences which often leads to other problems such as social exclusion, reduced opportunities to get back to work or study, and problems forming new relationships.[1,2]

Schizophrenia is a relatively common illness with an annual incidence of 15.2 per 100,000 people (range 4.4 to 33), and an estimated overall prevalence of 0.35% (range 0.2% to 0.59%).[2]

Antipsychotics are the mainstay of the treatment of schizophrenia. First-generation antipsychotics, whilst considered to be effective in the treatment of positive, psychotic symptoms, show little benefit in alleviating negative symptoms and the associated cognitive impairment. Second generation 'atypical' antipsychotics differ significantly in their pharmacological and clinical profiles and are generally considered to be effective against both the positive and negative symptoms of schizophrenia and with an superior safety profile with respect to extrapyramidal side effects.

NICE guidance recommends that a depot or long-acting injectable (LAI) antipsychotic medication should be offered to people with schizophrenia who would prefer such treatment after an acute episode, or where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan.[1] Depot antipsychotics are administered by deep intramuscular injection, which are then slowly released from the injection site to give relatively stable drug levels over long periods allowing injections to be given every few weeks. Of the seven atypical antipsychotic drugs available in the UK, four are available in depot injection preparations; olanzapine, risperidone, paliperidone and most recently aripiprazole.

Aripiprazole is an atypical antipsychotic, thought to act as a partial agonist at dopamine D_2 receptors and serotonin 5-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptors.[3] It is licensed for treatment of schizophrenia, as well as treatment and prevention of manic episodes in people with bipolar I disorder. Aripiprazole is available in tablets, orodispersible tablets and oral solution, as well as an intra-muscular injection intended for the rapid control of agitation and disturbed behaviour in patients with schizophrenia.[4,5] This short-acting injection is intended for short-term use only, and should be discontinued as soon as clinically appropriate in favour of oral aripiprazole.

A long-acting injection (LAI) formulation of aripiprazole (Abilify Maintena®, Otsuka Pharmaceuticals) launched in the UK in February 2014. It is licensed for the

maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.[6] Aripiprazole LAI has been approved for use in Scotland by the SMC, and in Wales by the AWMSG.[7,8]

Clinical evidence

The pivotal study was a randomised double-blind double dummy non-inferiority trial.[9] Patients were aged 18-60 years with a DSM-IV-TR diagnosis of schizophrenia for at least three years, and had a history of symptom exacerbation when not receiving antipsychotics. People with other DSM-IV-TR diagnoses other than nicotine and caffeine dependence were excluded, as were those with uncontrolled thyroid function abnormalities, a history of seizures, neuroleptic malignant syndrome, tardive dyskinesia, or other medical conditions considered to put the patient at undue risk or to affect study assessments.

The study had three phases:

- Phase I (4-6 weeks) – cross-titration from existing antipsychotic medication to oral aripiprazole, with a target dose of 10-15 mg daily. Patients already receiving aripiprazole entered the study at phase II.
- Phase II (8-28 weeks) – patients assessed fortnightly until stabilised on oral aripiprazole at a dose of 10-30 mg daily for 8 consecutive weeks. The definition of stability is listed in appendix A.
- Phase III (up to 38 weeks) – patients randomised 2:2:1 to receive aripiprazole LAI 400 mg monthly, oral aripiprazole 10-30 mg daily or aripiprazole LAI 50 mg monthly (included as a pseudo-placebo to confirm assay sensitivity). Patients in the aripiprazole LAI groups continued to receive oral aripiprazole 10-20 mg daily for 14 days following randomisation, in order to maintain therapeutic levels. A double-dummy design was used, such that all patients received an active injection and placebo tablets, or a placebo injection and active tablets.

Patients in the aripiprazole 400 mg LAI group were allowed a one-time reduction in dose to 300 mg if required to mitigate adverse effects. A one-time increase back to 400 mg was also permitted. Those receiving oral aripiprazole were permitted a one-time increase or decrease in dose and a one-time reversal of that change, as long as the dose remained in the range of 10-30 mg daily at all times.

A total of 709 patients were enrolled in phase I of the trial, with an additional 228 already on oral aripiprazole recruited directly to phase II. In total, 662 were eventually randomised in phase III. Most discontinuations before phase III were due to withdrawal of consent or unspecified reasons.

The primary outcome measure was the proportion of patients experiencing impending relapse (defined in appendix A) after 26 weeks double-blind treatment. Secondary outcomes included time to impending relapse, rate of impending relapse at week 38, proportion of responders (people meeting stability criteria), proportion of remitters (defined in appendix A), time to discontinuation, and scores on the PANSS, CGI-S and CGI-I scales (see appendix B for definitions).

After 26 weeks treatment, Kaplan-Meier estimates of impending relapse rates were comparable for aripiprazole 400 mg LAI (7.12%) and oral aripiprazole (7.76%). The estimated treatment difference was 0.64% (95% CI -5.26 to 3.99, p=0.79), confirming non-inferiority. The impending relapse rate with aripiprazole 50 mg LAI

was significantly higher than in either of the treatment groups (21.8%). There was no significant difference in the time to impending relapse between the 400 mg LAI group and the oral aripiprazole group.

There was no difference in the proportion of responders between the two active treatment groups, but the proportion was significantly lower in the 50 mg LAI group than with the 400 mg LAI. There was no significant difference in the incidence of remission; however patients who met the criteria for impending relapse were excluded from the denominator of that analysis.

There was no significant difference in PANNS, CGI-S or CGI-I scores between groups at baseline. By week 38, all scores were significantly better in the aripiprazole 400 mg LAI arm than in either of the other groups.

A second trial compared aripiprazole 400 mg LAI to placebo.[10] The design was similar to that outlined above, except that the cross-tapering phase lasted 4-6 weeks, and the oral stabilisation phase for 4-12 weeks. In phase III in this trial all patients received single-blind aripiprazole 400 mg LAI until stable for at least 12 consecutive weeks. In phase IV, patients were randomised 2:1 in a double-blind fashion to continue with aripiprazole or switch to placebo injection for 52 weeks. Antidepressants, mood stabilisers and antipsychotics other than aripiprazole were prohibited throughout.

A total of 843 people were eligible for inclusion, and 403 were eventually randomised in phase IV. The primary outcome was impending relapse, as defined in appendix A, and a pre-specified interim analysis after 64 primary outcome events found that aripiprazole was significantly more effective than placebo. The final analysis included 80 events and found that relapse rates were 10% in the aripiprazole group compared with 39.6% with placebo (HR 5.03, 95% CI 3.15 to 8.12).

The trial was terminated early on ethical grounds following the interim analysis, in order to limit patient exposure to placebo. Consequently very few patients completed the intended one year of treatment. Approximately one third of patients completed 6 months (7 aripiprazole injections) and 9% (n=26) completed the entire year.

Limitations

Due to a lower than expected event rate, the primary efficacy outcome of the pivotal trial was changed from time to impending relapse to proportion of people with impending relapse by week 26.[3,9] The EMA considered that a higher than expected mean age (41 years) and long oral stabilisation phase may have contributed to the low relapse rate.

While rates of discontinuation due to adverse events were low in the pivotal trial, the main reasons for stopping were withdrawal of consent and unspecified reasons. This may mask drop-outs due to adverse events. Drop-outs due to lack of efficacy were captured as primary trial outcome events.

Efficacy in the pivotal trial was assessed in the intention-to-treat (ITT) population. ITT analyses are considered conservative in superiority trials, because they tend to minimise the difference between treatment arms. However, in non-inferiority trials this may increase the risk of finding non-inferiority when a true difference exists. It is therefore good practice to present both ITT and per-protocol (PP) analyses of

efficacy in these trials.[11] While sensitivity analyses were carried out, it is not clear if a PP analysis was conducted. There was no statistical adjustment for multiple testing.[9]

The authors of the pivotal trial highlight that efficacy analysis was conducted in patients already stabilised on oral aripiprazole, and cannot be extrapolated to patients taking other oral antipsychotics.[9] This limitation is taken into account by the European product license, which specifies that Abilify Maintena® should only be used in adults stabilised on oral aripiprazole.[6] Trial participation was limited to patients with mild, chronic schizophrenia, which may limit the generalisability of the findings.

Use of the aripiprazole placebo and pseudo-placebo groups in the published trials raises ethical concerns. However, the EMA guideline on the development of medicinal products for schizophrenia recommends inclusion of a placebo arm to confirm assay sensitivity, due to changes in the diagnostic and efficacy criteria for schizophrenia over time. The placebo and pseudo-placebo arms are intended to confirm the sensitivity of the trial for the specified outcomes.

There are no available data on long-term efficacy, although the EMA considered that the double-blind periods in the above trials were of sufficient length to demonstrate efficacy for maintenance treatment. There are no comparisons against drugs other than oral aripiprazole, although trials comparing aripiprazole LAI with paliperidone LAI are ongoing, one of which is planned to last for 18 months.[12]

Safety

The EMA has reported pooled safety data from 1600 patients exposed to aripiprazole LAI, approximately 1000 of whom were exposed for at least 6 months.[3] No new safety concerns were identified compared to oral or rapid intramuscular formulations of aripiprazole. The exception was injection site pain, which was reported by 5.2% of patients receiving aripiprazole 400 mg LAI, compared to 0.8% receiving the 50 mg pseudo-placebo and 3.7% receiving true placebo.

The incidence adverse events was comparable between the 400 mg LAI and oral aripiprazole groups (73% vs. 80%). The only serious adverse events reported in >1% of patients were schizophrenia and psychotic disorder, which were considered related to the underlying disorder.

Extrapyramidal symptoms (EPS) and EPS-related events were more common with the 400 mg LAI than oral aripiprazole (18.4% vs. 11.7%) or the placebo group (9.7%). The incidence also increased with time. A post-authorisation study has been requested to further investigate this issue.

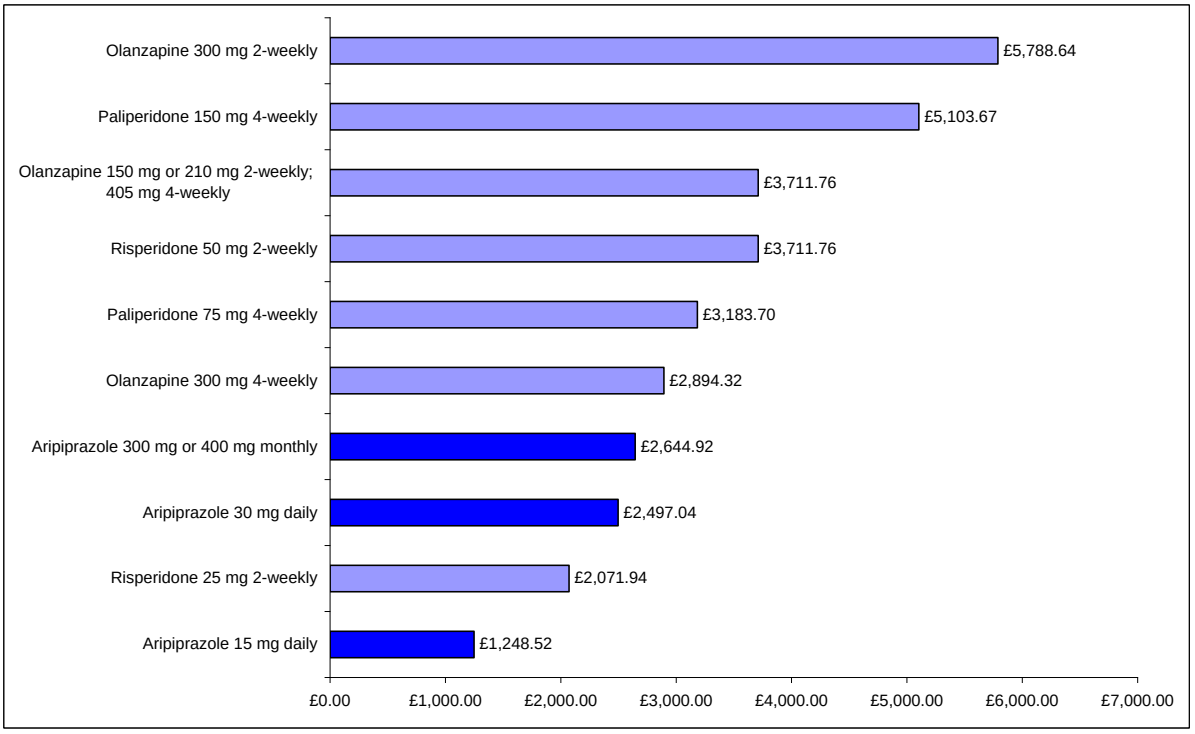
The incidence of clinically relevant weight gain (defined as ≥7% of starting body weight) was comparable between the 400 mg LAI and oral aripiprazole groups (15.9% vs. 16.2%). Clinically relevant weight loss (also ≥7% of starting body weight) was more common with the LAI than oral aripiprazole (15.2% vs. 10.2%).

The pivotal trial reported a higher incidence of low white blood cell count in the aripiprazole 400 mg LAI group compared with oral aripiprazole (2.3% vs. 0.8%). Although several patients had low baseline values the EMA considered that there was potential clinical significance, and the issue is highlighted in the product SPC.

Cost analysis

Aripiprazole LAI costs less than most other atypical antipsychotic depots (see chart below), but more than oral aripiprazole. Both 300 mg and 400 mg presentations have been authorised by the EMA, however the manufacturers have no plans to market the 300 mg product in the UK.[13] There will therefore be no difference in acquisition cost for patients who require a lower dose.

Figure 1: annual cost per patient of second-generation depot antipsychotics (dm+d/Drug Tariff, August 2014)



NB: costs are for comparison only and do not imply therapeutic equivalence. Oral aripiprazole included for reference.

The depot antipsychotics available in the UK are not licensed in the same populations:

- Aripiprazole (Abilify Maintena®, Otsuka Pharmaceuticals) and olanzapine (Zypadhera®, Eli Lilly) depots are only licensed in patients already stabilised on oral aripiprazole and olanzapine respectively.
- Paliperidone depot (Xeplion®, Janssen-Cilag) is licensed in patients stabilised on oral paliperidone or risperidone, or patients with mild to moderate psychotic symptoms requiring an injectable treatment and with previous responsiveness to oral paliperidone or risperidone.
- Risperidone depot (Risperdal Consta®, Janssen-Cilag) is licensed in patients stabilised with any oral antipsychotics.

A detailed economic comparison between them is therefore not appropriate. However, a summary of cost-effectiveness published by the SMC found that, taking into account administration costs, aripiprazole LAI was cheaper than both risperidone and paliperidone during both the initiation and maintenance phases (see table 1 below).[7] The maintenance phase was considered separately, since patients

starting therapy with aripiprazole or risperidone depots require concomitant oral medication at the start of therapy in order to maintain therapeutic levels. Paliperidone and olanzapine have no such requirement.

The analysis was very sensitive to drug acquisition costs, and lower doses of comparators were in some cases less expensive than aripiprazole. However SMC considered that the lower doses were not commonly prescribed, and analyses based on the most commonly prescribed doses favoured aripiprazole. Olanzapine was not included, but given its higher acquisition cost and requirement for dosing every two weeks, it is likely to also be more expensive.[6,14-16]

A similar analysis by the All Wales Medicines Strategy Group found that aripiprazole was associated with both a greater gain in quality-adjusted life years than risperidone and paliperidone, and reduced cost.[17]

Table 1: price comparison adapted from data published by the SMC

Treatment	Initiation phase	Maintenance phase
Aripiprazole	£2,997	£2,949
Risperidone	£3,633	£3,632
Paliperidone	£4,174	£3,807

Depot antipsychotics cannot be self-administered. Administration costs will also vary depending on the setting, and will be higher for preparations requiring more frequent injections. One hour of patient contact with a specialist mental health nurse costs £76, while one hour of patient contact costs £53 for a practice nurse.[18]

Each aripiprazole depot injection must be reconstituted immediately prior to administration (or a maximum of 4 hours in advance if stored below 25°C).[6] Olanzapine and risperidone have similar requirements (although may be stored for 24 hours following reconstitution).[14,15] In contrast, paliperidone is supplied as a suspension, and will therefore require less staff time to prepare and administer.[16] Cost will therefore vary depending not only on the setting of administration, but the time required to properly reconstitute each drug.

Risperidone depot must be stored at 2-8°C, which increases the risk of wastage in the event of cold chain breaches. The other products can be stored at room temperature.

Patient impact

Only two doses of aripiprazole depot have been licensed; all patients begin treatment with 400 mg monthly, with the dose reduced to 300 mg monthly if adverse reactions occur. The restricted doses may limit the number of patients for whom the depot is suitable. Aripiprazole has a more favourable adverse event profile than the other second-generation antipsychotics with available depot formulations, including a lower risk of weight gain.[19] While this may be appealing to patients, the product is only licensed in people already stable on oral aripiprazole and switching may not be appropriate.

Risperidone depots, and some doses of olanzapine, require 2-weekly administration, thus increasing the burden of treatment. The monthly administration of aripiprazole

may therefore be more convenient. Use of depot preparations has been found to reduce the incidence of schizophrenia relapse compared to oral medications, which is possibly attributable to increase adherence. It should be noted however that the data are limited due to methodological problems in the published trials.[20] Conversely, some patients may find the use of depot preparations disempowering, and prefer to pursue a treatment strategy over which they can have more control.

Concurrent oral aripiprazole is required at the start of therapy to ensure that therapeutic levels are maintained, which may be a source of inconvenience or confusion. Depot risperidone has the same requirement, while paliperidone and olanzapine do not. [14-16]

Points to consider

Aripiprazole is one of four second-generation antipsychotics available as depot injections. It is licensed for use as a monthly injection, only in patients already stabilised on oral aripiprazole. Aripiprazole depot was found to be non-inferior to oral aripiprazole for the prevention of relapse of schizophrenia after twenty-six weeks treatment in the licensed population.[9] A second study found it was superior to placebo for the same outcome, although the trial was terminated early on ethical grounds, to limit patient exposure to placebo.[10]

A pooled analysis of 1600 exposed patients, including 1000 who received at least 6 months treatment, did not find any new safety concerns compared to oral or rapid-acting intramuscular aripiprazole. The incidence of extra-pyramidal symptoms was higher with the 400 mg LAI than oral aripiprazole, and a post-authorisation study has been requested. While the incidence of weight gain was comparable between groups, clinically significant weight loss was more common with the 400 mg LAI than oral aripiprazole.

The acquisition cost for aripiprazole LAI is lower than the other licensed depot preparations. The administration cost will be lower than that for depots which must be administered every two weeks (such as risperidone and some doses of olanzapine). However due to differences in the licensed populations, detailed cost analysis is not appropriate.

It has been approved for use by both the SMC and AWMSG following economic evaluation. NICE have not produced guidance for this product, although they have published an evidence summary.[21] Use of antipsychotic depots may increase patient adherence and reduce the rate of relapse, however some patients may find the use of depots disempowering.

Author's declaration. The lead author has no relevant interests to declare.

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Appendix A: Definitions used in the clinical trials[9,10]

Stability

Stability on oral aripiprazole was defined as meeting the following criteria for 8 consecutive weeks:

- Outpatient
- PANNS total score ≤80 with a score of ≤4 (moderate) on each of the following items:
    - Conceptual disorganisation
    - Suspiciousness
    - Hallucinatory behaviour
    - Unusual thought content
- CGI-S score ≤4 (moderately ill)
- CGI-SS score ≤2 (mildly suicidal) on part 1 and ≤5 (minimally worsened) on Part 2

Impending relapse

Impending relapse was defined as meeting any or all of the following 4 criteria:

1) Clinical Global Impression of Improvement (CGI-I) of ≥ 5 (minimally worse) **and either**
    a) an increase on any of the following individual PANSS items
        i) conceptual disorganization
        ii) hallucinatory behaviour
        iii) suspiciousness
        iv) unusual thought content

        to a score > 4 with an absolute increase of ≥2 on that specific item since randomization **or**
    b) an increase on any of the following individual PANSS items
        i) conceptual disorganization
        ii) hallucinatory behaviour
        iii) suspiciousness
        iv) unusual thought content

        to a score >4 and an absolute increase of ≥4 on the combined 4 PANSS items since randomization;
2) Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), but excluding hospitalization for psychosocial reasons;
3) Clinical Global Impression of Severity of Suicide (CGI-SS) of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2
4) Violent behaviour resulting in clinically relevant self-injury, injury to another person, or property damage.

Remission:

A score of ≤3 on each of the following eight PANSS items, maintained for a period of 6 months:

1. delusions
2. unusual thought content
3. hallucinatory behaviour
4. conceptual disorganisation
5. mannerisms/posturing
6. blunted affect
7. social withdrawal
8. lack of spontaneity

Appendix B: Rating scales used to assess schizophrenia signs and symptoms

Clinical Global Impression (CGI)[22]

The CGI was developed for research purposes. All domains are rated on a scale of 1 (least severe) to 7 (most severe). Domains used above were:

- CGI Severity (CGI-S): Considering your total clinical experience with this particular population, how mentally ill is the patient at this time? Rated on a scale of:
    - 1 = normal, not at all ill, to
    - 7 = among the most extremely ill patients.
- CGI Improvement (CGI-I): Compared to the patient's condition at admission to the project, this patient's condition is (rated on a scale of):
    - 1 = very much improved, to
    - 7 = very much worse

Positive and Negative Syndrome Scale (PANSS)[23]

PANSS is a 30-item scale with 3 domains. Each item is scored from 1 (absent) to 7 (extreme), resulting in a minimum score of 30 and a maximum of 210.

- Positive scale (7 items, min. score 7, max. score 49)
    - Delusions
    - Conceptual disorganisation
    - Hallucinatory behaviour
    - Excitement
    - Grandiosity
    - Suspiciousness
    - Hostility
- Negative scale (7 items, min. score 7, max. score 49)
    - Blunted affect
    - Emotional withdrawal
    - Poor rapport
    - Passive-apathetic social withdrawal
    - Difficulty in abstract thinking
    - Lack of spontaneity and flow of conversation
    - Stereotyped thinking

General psychopathology scale (16 items, min. score 16, max. score 112)

- Somatic concern
- Anxiety
- Guilt feelings
- Tension
- Mannerisms and posturing
- Depression
- Motor retardation
- Uncooperativeness
- Unusual thought content
- Disorientation
- Poor attention
- Lack of judgement and insight
- Disturbance of volition
- Poor impulse control
- Preoccupation
- Active social avoidance