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Project BETA (Best Practices for Evaluation and Treatment of Agitated Patients)

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Agitation is an acute behavioural emergency that requires immediate intervention to prevent complications and to establish a therapeutic relationship (Table 1). In general, emergency psychiatric care aims to fulfil six goals (Table 2) (1). These are part of the full evaluation and treatment of agitation. First, effective triage and screening is called for, to exclude medical causes of the agitation symptoms. Due to medical reasons or intoxication, many situations can present with agitation, potentially mimicking the psychiatric illness. The next goal is to rapidly relieve a patient's suffering, and to achieve this in a way that is non-coercive and takes place in the least restrictive setting.

This means that, ideally, the patient is willing to take medication, and the use of restraints can be avoided. Physicians should form a therapeutic alliance with their patients, so that they will collaborate with healthcare providers and trust them, rather than fear them. If patients experience non-coercive relief from their symptoms, they will be more likely to continue with their outpatient treatment in the future, to be comfortable with the mental health system, and not to shy away from seeking help in Project BETA (Best Practices for Evaluation and Treatment of Agitated Patients) time. Once agitation has been stabilised, appropriate disposition of the patient and aftercare should be ensured, to prevent agitation from recurring in the future.

The preferred intervention for calming agitated patients is verbal de-escalation. Unless signs and symptoms dictate emergency medical intervention, de-escalation must take precedence in an effort to calm the patient. Non-pharmacological approaches should be applied first. Medication can help and can be offered as a part of verbal de-escalation. Drugs should not be used as chemical restraints, but appropriate agents should be chosen to treat symptoms. Medication is used to calm the patients and not to induce sleep. The patients should be involved in the process of selecting medication. Oral medications are to be preferred over intramuscular administration.

The goal of de-escalation is to help the patients regain control, so that they can participate in their evaluation and treatment. Successful de-escalation is the key to avoiding seclusion and restraint. While engaging the patients in verbal de-escalation, the clinicians' observations and medical judgment must drive decisions regarding the management of the patients.

Verbal de-escalation is the centrepiece of the BETA project, and it is part of all of the aspects of agitation evaluation and treatment. It usually takes less time than the process of restraint and involuntary medication. Discussions during the BETA project have shown that verbal de-escalation can typically be effective in five to ten minutes or less. On the other hand, takedowns, placing under restraint, preparation of syringes, and injection of medications can take far longer, as much as 15 to 20 minutes. It is helpful for healthcare professionals who feel they are typically 'too busy' to try de-escalation, to learn that this can actually be a time saver.

Also, avoiding containment procedures will result in fewer injuries to both staff members and patients. Patients are more trustful when not restrained or forcibly medicated. Furthermore, receiving facilities will be more willing to accept a patient who has not been restrained, which improves throughput. Many psychiatric hospitals or inpatient units either will not consider taking a person in under restraint, or will want them to be out of restraint for a substantial period prior to accepting the patient for transfer.

Table 1: Goals in the treatment of agitation

• Reduce dangerous behaviours, distress, anguish
• Minimise side effects
• Calm to tranquility, not to unconsciousness
• Minimise the need for physical restraint
• Treat while creating a therapeutic alliance
• Help to decrease future episodes of acute agitation

Table 2: The six goals of emergency psychiatric care (1)

• Exclusion of medical aetiologies of symptoms
• Rapid stabilisation of the acute crisis
• Avoidance of coercion
• Treatment in the least restrictive setting
• Formation of a therapeutic alliance
• Formation of an appropriate disposition and aftercare plan

(1) Zeller SL, Primary Psychiatry 2010; 17(6): 35-41

Clinical management of agitation through a continuum

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Agitation is defined as a non-specific constellation of relatively unrelated behaviours that can be seen in a number of clinical conditions, and that usually shows a fluctuating course. Patients with psychomotor agitation display excessive verbal and/or motor activity (1). As opposed to this, aggression is an overt behaviour that involves the intention to inflict noxious stimulation or to behave destructively towards other persons or objects (including auto-aggression). Agitation represents a continuum, in which patients move from quiet negativism to overt hostility (2, 3).

Organic and non-organic mental disorders (psychotic and nonpsychotic) are the underlying causes. The pathophysiological mechanism underlying the psychosis, and possibly the agitation, is believed to be hyperdopaminergia in the basal ganglia, increased noradrenergic tone, or reduced GABAergic inhibition (1). It has also been suggested that some serotonergic pathways can modulate dopaminergic activity in cortical areas through 5-HT2A receptors. This mechanism might explain the beneficial effects on extrapyramidal symptoms of antipsychotics with pronounced 5-HT2A antagonism.

Table: Main objectives when working with an agitated patient

• Ensure the safety of the patient, staff, and others in the area
• Help the patient manage his/her emotions and distress, and maintain or regain control of his/her behaviour
• Avoid the use of restraints whenever possible
• Avoid coercive interventions that can escalate agitation

Patients with agitation describe their experience as explosive and/or unpredictable anger, restlessness, pacing, excessive movement, physical and/or verbal self-abuse, and demeaning or hostile verbal behaviour. They are uncooperative, resistant to care, demanding, impulsive and impatient, and they show low tolerance to pain and frustration. Without treatment, agitation can rapidly escalate to aggressive, threatening and violent behaviour.

Agitation can be prevented or ameliorated using verbal intervention, activities/non-verbal therapy, and medication (4). Patients prefer not to undergo either forced medication or seclusion/physical restraint. The clinical symptoms of agitation need to be taken seriously, as a sign of suffering as well as a risk factor for aggression and coercion.

According to an expert consensus on the ideal treatment for agitation, a non-coercive/collaborative approach in the form of verbal de-escalation is required (2). Symptom escalation should be avoided. Traditional methods of routine restraints and involuntary medication should be replaced, with much greater emphasis on a non-coercive approach (3). The new paradigm consists of a three-step approach:

1. The patient is verbally engaged;
2. A collaborative relationship is established;
3. The patient is verbally de-escalated out of the agitated state.

There are four main objectives when working with agitated patients (Table). If verbal de-escalation is not successful, first-line medical treatment is administered orally (Figure). This allows for maintenance of the patients' collaboration and commitment to their treatment, while calming them rapidly. The available medications include first-generation antipsychotics (FGAs; haloperidol, phenotiazines, loxapine), second-generation antipsychotics (SGAs; oral aripiprazole, olanzapine, risperidone; intramuscular aripiprazole, olanzapine, ziprasidone), and benzodiazepines. As compared to FGAs, SGAs have similar efficacy, but a decreased risk of dystonia, akathisia, and extrapyramidal symptoms. Inhaled antipsychotic treatment is possible with loxapine and provides a rapid onset of action. A substantial proportion of bipolar disorder patients responds to loxapine treatment within ten minutes, and after two hours, the majority of patients shows a response [5]. In severe agitation, when all other options have been exhausted, intramuscular treatment and restraints are necessary.

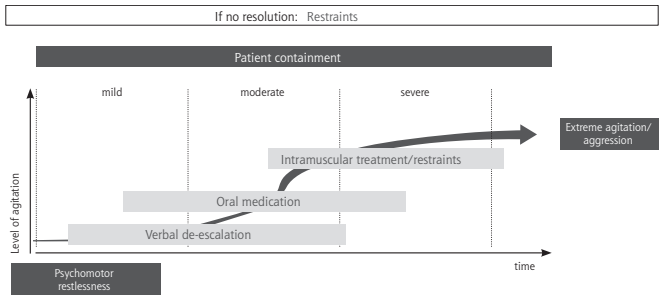

Figure: Expert consensus on the optimal treatment for agitation (2)

(1) Lindenmayer JP, J Clin Psychiatry 2000; 61(suppl 14):5-10
(2) Allen MH et al., J Psychiatr Pract 2005; 11 Suppl 1:5-108; quiz 110-112
(3) American Association for Emergency Psychiatry Project BETA De-escalation Workgroup; West J Emerg Med 2012 Feb; 13(1):17-25
(4) van de Sande et al., Br J Psychiatry 2011; 199(6):473-478
(5) Kwentus J et al., 2012 Bipolar Disord 2012; 14(1):31-40

Rational and well-established use of loxapine in the treatment of agitation

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Agitation is a complex entity. On the psychopathological level, for an individual, agitation might be conceived as a sudden reduction in adaptive behavioural capabilities, or as an attempt to add a new means of communication. For the course of the disorder, agitation can be seen as a parenthesis, a fugitive epiphenomenon that can be considered exceptional, or as a turning point, as an opening towards significant and positive changes. With respect to treatment goals, agitation requires quick sedation, to allow rapid referral to an adequate psychiatric facility. A certain period of time is required to examine and choose the optimal final patient management.

Good management of agitation improves the overall course of the disorder. Mental disorders are chronic conditions in the course of which some periods are crucial. Good management of these periods can increase insight into the disorder, adherence to care, compliance to medication, and family cooperation. Agitation is one of these periods, either as a first episode or as a relapse. Not all relapses are identical. The challenge for clinicians is to improve the outcome in the context of agitation.

Loxapine has been in use for 35 years. A Cochrane review of 41 randomised, placebo-controlled trials indicated the proven efficacy and good safety profile of loxapine in patients with schizophrenia [1]. In this review, loxapine was shown to be as effective as atypical antipsychotics, and as effective as typical antipsychotics in the short term. Open-label reports confirm these observations. Gaussares et al. emphasised the rapid action and good haemodynamic tolerance of loxapine (2). Moritz et al. noted that it provides effective sedation in agitation, although rare undesirable effects can occur with intramuscular application of loxapine 200mg: two of 67 patients developed acute dyskinesia, and nine developed low blood pressure (3).

The French guidelines on the treatment of agitation recommend loxapine treatment whenever chemical sedation is called for (Figure). In France, loxapine is used for the treatment of agitation in a variety of conditions: as a rapid-acting antipsychotic in active hallucination and in delirium associated with agitation in patients with both schizophrenia and bipolar disorder; as an antiexcitatory medication for patients with manic thoughts and agitated behaviour, and for those with accelerating mental and motor processes induced by toxic substances, such as amphetamines; as a rapid tranquiliser in patients with motor agitation, independent of the cause; and as an anxiolytic for patients with anxiety associated with agitation and psychosis. The last is true in particular for psychotic patients, whose agitation appears to be closely related to anxiety.

Due to the rapid action and good safety profile of loxapine, this drug is used in psychiatric patients with comorbid conditions, such as alcohol or drug abuse, for the treatment of agitation and behavioural disturbances associated with drug or alcohol use only, in young patients to prevent negative connotations of their first experience of medical treatment, and in agitation and anxiety in patients with borderline personality. In patients who are psychotic or have bipolar disorder with partial adherence to treatment, loxapine is perceived as a rescue medication in addition to the patients' main psychiatric treatment.

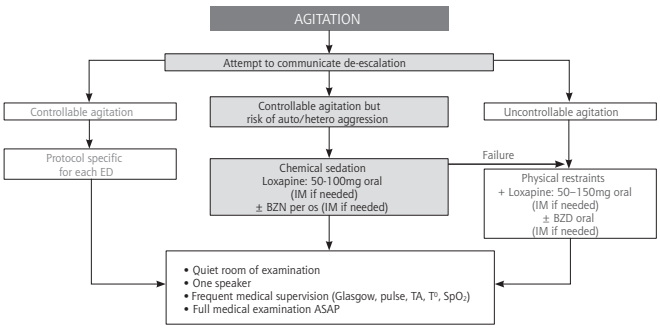

Figure: French guidelines on the treatment of agitation

(1) Chakrabarti A et al., Cochrane Database Syst Rev 2007 Oct 18; (4):CD001943
(2) Gaussares C et al., Inf Psychiatr 1989; 69:656-660
(3) Moritz F et al., Presse Med 1999; 28(30):1630-1634

An update on acquired choreatic disorders

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Genetic choreas need to be differentiated from non-genetic choreas (1). There are a number of causes of the non-genetic disease (Table). At a tertiary centre in Milan, Italy, non-genetic choreas were studied in 42 adult patients, between 1994 and 1999 (2). Stroke was identified as the most common cause (21/42), followed by drug use (7/42) and AIDS (5/42). Hyperglycaemia, hyponatriaemia and hypoxia were the cause of chorea in two cases each, while borreliosis, vasculitis and Sydenham's chorea were causative in one case each.

Hemichorea-hemiballism is predominantly due to vascular lesions. Most lesions occur outside the substantia nigra. Type-2 diabetes is a common risk factor. Spontaneous resolution has been observed. Management includes the administration of dopamine receptor blockers and tetrabenazine, as well as surgery. Chorea often precedes the diagnosis of systemic lupus erythematodes. Management recommendations include neuroleptics, steroids and anticoagulant treatment.

For non-genetic chorea in children, a study conducted between 1980 and 2004 at a tertiary center in Pittsburgh, USA, found Sydenham's chorea to be the most common cause (79/82) (3). The remaining infrequent causes included basal ganglia stroke (two cases) and postoperative ischaemic brain changes (one case). Sydenham's chorea starts in childhood; in 20% of cases, it manifests as hemichorea (4). Recurrence can occur spontaneously, or it can be triggered by pregnancy or use of contraceptive agents. Behavioural changes include attention deficit/hyperactivity disorder, obsessive-compulsive disorder, and dysexecutive syndrome. Treatment consists of the administration of valproic acid, neuroleptics, and steroids.

Table: Different types of non-genetic choreas according to causes (1)

• Drug-induced chorea
• Vascular chorea
• Infectious chorea
• Immunological chorea
• Endocrine-metabolic chorea
• Miscellaneous chorea

(1) Cardoso F et al., Lancet Neurol 2006; 5(7): 589-602
(2) Piccolo I et al., J Neurol 2003; 250:429-435
(3) Zomorrodi A & Wald ER, Pediatrics 2006; 117(4):e675-e679
(4) Cardoso F, Neurol Clin 2009; 27(3):719-736

Loxapine – a possible solution for managing aggression in the manic patient

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A41-year old female had already undergone approximately 20 hospitalisations due to bipolar I affective disorder, after her first episode in 1999. Due to her violent behaviour, most of these hospital admissions had been compulsory. The patient frequently displayed psychotic symptoms during her manic episodes. She mostly had paranoid ideas, and infrequently developed optic and/or acoustic hallucinations.

Previous psychiatric therapy had included lithium, antiepileptic therapy, a range of antipsychotics, antidepressants, various benzodiazepines, and electroconvulsive therapy. During previous admissions, intramuscular (i.m.) zuclopenthixol, i.m. haloperidol, and intravenous and i.m. benzodiazepines had been applied, in terms of her aggressive behaviour and agitation, and when the patient refused to take her oral medication. Basically, the patient responded well, but she did not accept the parenteral administration well.

At the time of the current admission, her Young Mania Rating Scale (YMRS) score was 42. Oral therapy with olanzapine, lithium and diazepam was started. However, the patient experienced no significant reductions in manic symptoms, and she had difficulties complying. Loxapine, which is indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults, was administered twice in one day. Antimanic effects were seen after the first application for just one hour, and after the second application for 24 hours. After the second dose, her YMRS score had decreased to 17 points. Two days later, the treatment was administered once, producing antimanic effects for one hour. The patient received additional therapy with zuclopenthixol and diazepam. She experienced a metallic taste with the loxapine administration, but this did not keep her from taking it again. She felt calmer and 'eager' to try the new substance. The medical staff reported that after the second administration, the patient appeared considerably calmer and more compliant. No mechanical restraint was necessary.

Pharmacological treatment of schizophrenia across the life cycle

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The main principles of schizophrenia treatment apply to all phases of the disease, although the focus shifts between specific interventions. Attenuated psychosis syndrome represents an early stage. These patients show delusions and/or hallucinations and/or disorganised speech in an attenuated form, but the symptoms are of sufficient severity to warrant clinical attention. They cannot be explained by the presence of another mental disorder, and no criteria for other psychotic disorders have ever been met.

Interventions at the prodromal stage include treatment with antipsychotics, antidepressants, cognitive behavioural therapy, and omega-3 fatty acids. Clinical monitoring is essential. These measures are aimed at reducing the symptom burden and disability, and preventing the conversion into manifest schizophrenia. A meta-analysis of interventions at the prodromal stage has shown a reduction in the risk of transition of 35% (1). On the other hand, this treatment can be inappropriate, and cause side effects as well as stigmatisation. In individuals at ultra-high risk for psychosis, a clinical staging model has been proposed (2). It is recommended to apply more benign interventions at first, such as cognitive behavioural therapy or supportive measures, and to progress to more intensive interventions if the patient does not improve (e.g., antipsychotics, antidepressants).

First-episode schizophrenia represents a critical period that determines the further development of the disease. After the acute treatment response, remission is possible, but also partial response and a chronic relapsing course can occur (Figure) (3,4). Early intervention is crucial to treat the psychiatric symptoms, to manage behavioural problems (e.g. agitation/ hostility; suicide), to reduce neurotoxicity, and to avoid sociotoxic consequences. A therapeutic relationship should be established as soon as possible. There should be a strong focus on psychoeducation, and adherence-enhancing measures should be enforced. For treatment, the first choice are new-generation antipsychotics, with doses at the lower end of the efficacy range.

In patients with chronic relapsing schizophrenia, relapse preventionis the primary goal. It is still a matter of debate whether antipsychotics improve primary negative symptoms at all. Adjunctive treatments can offer some benefit, such as selective serotonin reuptake inhibitors. Depot antipsychotics should be considered. Additionally, the patient should be engaged in nonpharmacological treatments. Again, adherence-enhancing measures are of great importance.

Late-life schizophrenia has a low prevalence of 0.1%–1%, and mainly females are affected. Basically, the same diagnostic criteria apply as for younger patients, but positive symptoms tend to be more variable. There have been only a few age-specific randomised controlled trials. Several criteria enable the physician to differentiate dementia from schizophrenia (Table) (5). In the management of these patients, the focus should be on dose and drug safety of antipsychotics, as the pharmacokinetics are different in the elderly: protein binding, hepatic metabolism and glomerular filtration rate are decreased, whereas distribution volume is increased. Adverse events tend to occur more frequently. General recommendations pertain to the use of lower doses (up to one third of the regular recommended dose) and slow dose increases. All routes of application are possible. There should be specific attention on interactions between drugs. A similar risk of metabolic side effects as in younger patients can be expected. With respect to cardiovascular and cerebrovascular complications, the treatment should be chosen based on the physical condition of the patient. The best evidence has been obtained for risperidone, olanzapine and quetiapine. Although elderly patients generally respond well to treatment, remission is more difficult to achieve.

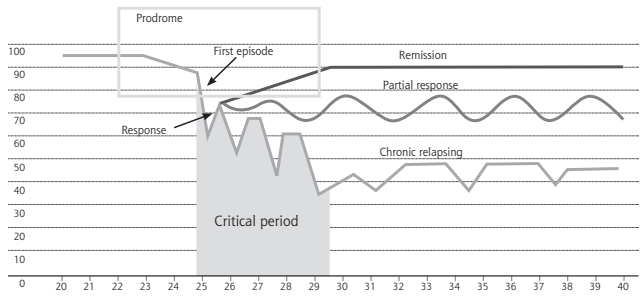

Figure: Possible outcomes after acute treatment response in first-episode schizophrenia (3,4)

Table: Differential diagnosis of dementia and schizophrenia (5)

	Dementia	Schizophrenia
Onset	usually at a later age	70% affected < age 40
Course	slowly progressive	usually in episodes
Cognitive impairment	starts with memory impairment, slowly progressive, global deficit at later stage	global deficits already early little, if any, progression
Orientation	usually impaired	mostly intact, even when disorganized
Affect	labile, but adequate	flat, inadequate, independent of situation
Psychomotor impairment	progressive slowing	episode-depending, fluctuating between hyperactivity and inhibition
Hallucinations	only at late stages, often optical	usually acoustic
Delusions	only at late stage, understandable content	bizzare, illogical

(1) van der Gaag M et al., Schizophr Res 2013; 149(1-3): 56-62
(2) McGorry PD et al., J Clin Psychiatry 2009; 70(9): 1206-1212
(3) Breier A et al., Am J Psychiatry 1994; 151: 20-26
(4) Birchwood M et al., Br J Psych 1998; 172 (33): 53-59
(5) Walter 2009

Hot topics in acute and long-term therapy of schizophrenia using antipsychotics

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An overview of meta-analyses showed that antipsychotic drugs are generally as efficacious as drugs used in other medical specialities (1). Relapse prevention with antipsychotics also has one of the largest effect sizes of drugs compared to placebo in medicine. A network meta-analysis of 212 antipsychotic drug trials in more than 40,000 participants came up with evidence-based hierarchies of the antipsychotic drugs analysed in various efficacy and side-effect domains in acute treatment (2).

A meta-analysis of 65 trials with 6,493 patients that compared antipsychotic drugs with placebo suggested that even in firstepisode patients and in fully remitted patients, relapse prevention should not be neglected (3). First-episode patients benefitted as much from maintenance treatment as multiple-episode patients. This means that even remitted patients cannot be considered cured, but rather need maintenance treatment. Still, the problem remains that those 20% of first-episode patients who do not experience a second episode cannot be identified in advance, and will therefore be treated unnecessarily.

Regarding the question of the optimal duration of antipsychotic treatment, it was shown that even patients who had been Hot topics in acute and long-term therapy of schizophrenia using antipsychotics stable for three to six years before the start of the study can relapse after withdrawal of medication. However, as this was a small group, any recommendation is tentative. For the time being, it can be said that multiple-episode patients should receive maintenance treatment for at least 3 to 6 years. The strategy of intermittent treatment, i.e., stopping antipsychotics once the patients are in remission, and only restarting them when early warning signs appear, has been ruled out by various randomised trials. Recent data by the group of Wunderink suggested that in first-episode patients, a similar strategy, called 'guided discontinuation', is an option (4).

There are recent controversial data on whether antipsychotic drugs cause brain volume loss (5). A naturalistic cohort of firstepisode patients with schizophrenia was followed up for 15 years. Here, it was shown that the group that had received the highest dose also had the most pronounced brain tissue loss, as measured by magnetic resonance imaging. The potential confounder that these patients were also the most severely ill ones was statistically controlled for. Thus, this study implied that high doses are deleterious for patients with schizophrenia. However, the same working group later published another analysis of the same cohort, which showed that the amount of brain tissue loss over time was also positively correlated with the duration of relapse. This suggests the importance of implementing proactive measures that can prevent relapse and improve treatment adherence. These data shed light on a troublesome dilemma that clinicians face: relapse prevention is important, but it should be performed using the lowest possible doses that will control the symptoms.

Another important randomised controlled trial examined whether it is possible to remove one antipsychotic if the patient is being treated with a combination of two or more drugs (6). It was shown that compared to patients who stayed on polypharmacy, a greater proportion of patients who switched to monotherapy needed medication change later on (usually they went back to polypharmacy). However, there was no difference in Positive and Negative Syndrome Scale (PANSS) total scores (Figure) or other outcomes. Moreover, the reduction group experienced significant improvements in metabolic parameters. The authors therefore recommend that attempts should be made to reduce antipsychotic combinations, most of which are not supported by randomised evidence either, in order to reduce the side-effect burden.

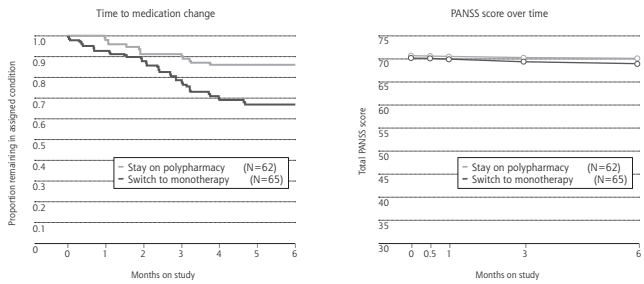

Figure: Switching from antipsychotic polypharmacy to monotherapy vs. staying on polypharmacy (6)

(1) Leucht S et al., Br J Psychiatry 2012; 200(2):97-106
(2) Leucht S et al., Lancet 2013; 382(9896):951-962
(3) Leucht S et al., Lancet 2012; 379(9831):2063-2071
(4) Wunderink L et al., J Clin Psychiatry 2007; 68(5):654-661
(5) Andreasen NC et al., Am J Psychiatry 2013; 170(6):609-615
(6) Essock SM et al., Am J Psychiatry 2011; 168(7):702-708

What to consider when using neuroleptic agents

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Neuroleptics are the gold standard treatment for patients with schizophrenia and acute mania. Also, they are widely used in the management of non-psychotic disorders and behavioural symptoms in dementia. Owing to their lower risk of extrapyramidal symptoms (EPS), atypical antipsychotics are now preferred over classical neuroleptics for most indications.

However, many safety issues remain unresolved. In addition, atypical antipsychotics are not a homogenous group of drugs, but vary widely in terms of receptor profile and side-effect profile. Cardiometabolic side effects (Table) are even more common with certain atypical agents than with classical antipsychotics. Nowadays, these side effects are the main concern. Clozapine, the drug with the best antipsychotic efficacy, and olanzapine are the agents with the highest risk for weight gain and diabetes mellitus (1). Prolongation of the QT interval can contribute to the increased risk of sudden cardiac death in patients taking antipsychotics. Clozapine in particular, and also old low-potency drugs, increase the risk of venous thromboembolism (2).

The management of metabolic risks conferred by antipsychotic therapy includes assessment of the patient's history of diabetes, dyslipidaemia, smoking, arterial hypertension, and cardiovascular disease. Weight, triglyceride levels, HDL/LDL cholesterol levels, glucose levels and blood pressure should be monitored. In at-risk subjects, the choice of antipsychotics with a lower metabolic side-effect profile is recommended.

Neurological side effects comprise sedation, cognitive decline, confusion/delirium, orthostatic hypotension, and acute EPS (acutedystonia, neuroleptic-induced Parkinsonism, acute akathisia). Tardive neuroleptic-induced movement disorders that are caused by long-term neuroleptic treatment or that persist after withdrawal include classic tardive dyskinesias, tardive dystonia, tardive tics, and others. The annual incidence rate of tardive dyskinesias in patients on classical antipsychotics is approximately 5% in adults and 25% to 30% in elderly subjects (Figure) (3). Prevention is the most important consideration in this context.

Classical neuroleptics have the highest risk for acute dystonia. With atypical agents, the risk for EPS is lower than with classical antipsychotics, but it is not negligible. Akathisia is one of the most common side effects of classical neuroleptics, although it can also occur with atypical antipsychotics, especially in patients with bipolar disorder. Individual risk factors for the manifestation of movement disorders associated with neuroleptic treatment have to be considered, such as age and gender. Moreover, neuroleptic-induced movement disorders are closely linked to the dopamine D2 receptor blocking properties of these drugs. The potency of a neuroleptic to induce EPS correlates with its D2 receptor affinity (4). Overall, the specific antipsychotic for the individual patient should be chosen based on the receptor and adverse event profile of the drug, and the clinical circumstances. Dosing has to be taken into account as well.

If tardive dyskinesia is already present, treatment includes withdrawal, dose reduction, and replacement by neuroleptics with lower D2 receptor affinity, especially clozapine (5). Tetrabenazine, amantadine, propranolol, benzodiazepines, levetiracetam, vitamin B6, and gingko can be used. Tardive dystonia is rare, but it is more disabling than classical tardive dyskinesia. Anticholinergics can be considered in these patients, although they are likely to cause worsening of chorea. Further treatment options include tetrabenazine, baclofen, clozapine, clonazepam, botulinum toxin in focal tardive dystonia, and deep brain stimulation.

Table: Side effects of neuroleptics

- Metabolic side effects:
  - weight gain
  - dyslipidaemia (trigylceride levels , HDL cholesterol)
  - insulin resistance
  - type-2 diabetes
- Cardiovascular events and mortality
- Sudden cardiac death
- Prolonged QT interval
- Orthostatic hypotension, arterial hypertension
- Venous thromboembolism
- Myocarditis
- Hyperprolactinaemia

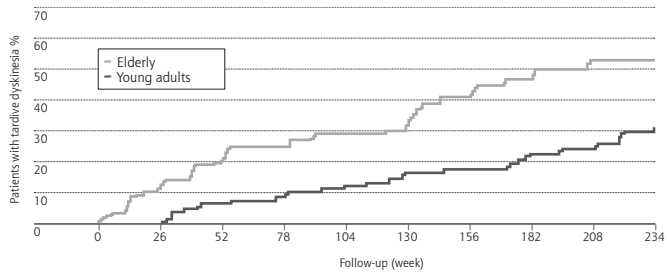

Figure: Annual incidence of tardive dyskinesias in patients treated with classical antipsychotics dependent on age (3)

(1) Leucht S et al., Lancet 2013; 382 (9896):951-962
(2) Masopust J et al., Psychiatry Clin Neurosci 2012; 66:541-552
(3) Saltz BL et al., Prim Care Companion J Clin Psychiatry 2004; 6(Suppl 2):14-19
(4) Kapur S & Seeman P, Am J Psychiatry 2001; 158:360-369
(5) Cloud LJ et al., Neurotherapeutics 2014; 11:166-176

Are antipsychotic-induced movement disorders still an issue?

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Antipsychotic-induced movement disorders are still an issue. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5, acute dystonia is defined as abnormal and prolonged contraction of the muscles of the eyes, head, neck, limbs, or trunk that develops within a few days of starting or raising the dose of a medication, such as a neuroleptic, or after reducing the dose of a drug used to treat extrapyramidal symptoms. Neuroleptic-induced Parkinsonism includes Parkinsonian tremor, muscular rigidity, akinesia, and bradykinesia. In acute akathisia, the patient complains of restlessness, which is often accompanied by excessive movement.

Tardive dyskinesia is defined as involuntary athetoid or choreiform movements of the tongue, lower face and jaw, and extremities. Tardive dystonia and tardive akathisia are distinguished by their late emergence in the course of treatment, and their potential persistence for months to years. Neuroleptic malignant syndrome is characterised by hyperthermia, generalised rigidity, and changes in mental status (delirium or altered consciousness, ranging from stupor to coma). Autonomic activation and respiratory distress are observed.

The manifestation of antipsychotic-induced movement disorders can be prevented by careful choice of drug and the use of slow dose increases, while keeping the dose as low as possible. Patients and carers should be informed about the risks of tardive syndromes, and self-monitoring should be encouraged. If movement disorders are already present, the dose should be lowered if possible. Anticholinergic agents can be added. Switching the antipsychotic is an option. Patients with akathisia benefit from the administration of betablockers. In neuroleptic malignant syndrome, intensive care monitoring/measures and dantrolene application are necessary. In tardive syndromes, the antipsychotic and anticholinergic treatment should be discontinued, if possible, and tetrabenazine should be added. Switching to clozapine or quetiapine is recommended. For the most part, extrapyramidal symptoms are preventable and treatable, if they are recognized; in this respect, there is room for improvement.

Bipolar affective disorder: which possible interactions to consider?

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The development of bipolar affective disorder requires the presence of vulnerability, which is due to genetic and inborn factors on the one hand, and psychological and social traumatic factors on the other. If vulnerability is present in a patient, distress can trigger the onset of the disorder, which can evolve to full-blown disorder. Therapeutic interventions can affect this evolution, such as pharmacotherapy, psychotherapy and sociotherapy. Also, individual resilience and a supportive environment can modify the course of the disease. From the neurobiological point of view, interactions of mood with the circadian rhythm are important. Synchronisation of this rhythm is guided by the hypothalamus. Bright light, physical activity and social activities influence the timing of the circadian rhythm.

As mood stabilisers are not enough to sustain remission in 20% to 40% of patients with bipolar affective disorder, psychotherapeutic approaches must be applied in combination with medication. In these patients, psychotherapy is aimed at increasing adherence to medication and improving psychosocial functioning between episodes (1). Also, treatment goals include the reduction of worries associated with the disorder, and decreases in the severity and length of episodes. The main approaches comprise expressed emotions in family members, social skills training, monitoring of warning signs, disruption of social rhythms and the sleep/ wake cycle, and changes in the level of cognitive schemes (2).

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Between mania and depression – is there more?

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From the genetic perspective, a better understanding of the individual risks should improve the management of bipolar disorders, by enabling researchers to design drugs for specific genetic subtypes of patients. For instance, a large-scale genomewide association analysis of bipolar disorder identified a new susceptibility locus near ODZ4 (1).

Another issue of interest is the influence of temperament on the burden of cyclothymia. Temperament is the emotional and affective basis of the personality. According to the concept of vulnerability, certain temperaments predispose to certain diseases. In patients with bipolar I, two temperamental dimensions can be observed: cyclothymia (emotional instability) and hyperthymia (emotional intensity) (2). As the pathoplastic model of temperament shows, mood swings follow different patterns in these two types of patients (intra-bipolar dichotomy; Figure). Also, the presence of a cyclothymic temperament predicts psychoactive substance use (3) and a less favourable course of alcohol dependence, with early onset and frequent relapses (4). Therefore, assessment of temperamental traits can be helpful for the prediction of the individual burden of disease.

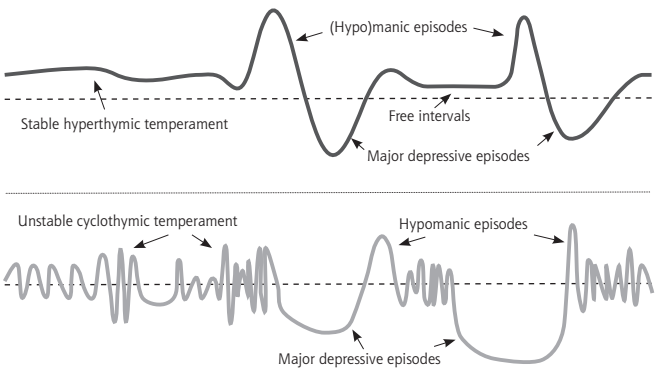

Figure: The pathoplastic model of temperament: intra-bipolar dichotomy

Mixed states of bipolar disorder have been described for more than 100 years. Depending on the definition used, the incidence of depressive symptoms in manic episodes is estimated at 30% to 40%. In the study by Vieta et al., 64% of patients who experienced a manic episode reported feeling depressed (5). Seventy-two percent of patients who experienced mania with depressive symptoms suffered from anxiety, irritability and agitation. Mixed states are a severe presentation of bipolar disorder; as compared to patients with non-mixed bipolar disorder, these patients experience more episodes and hospitalisations (6). Also, when compared to patients with pure mania, their dissatisfaction with life and their work impairment are more pronounced (7). Moreover, patients with mania and depressive symptoms have a considerably increased risk of suicide (8).

It is of clinical and scientific importance to recognise and identify symptoms of the opposite pole. Systematic assessments for these symptoms might assist diagnosis. The combination of anxiety and irritability or agitation during a manic episode can be used as a relevant discriminator for the presence of depressive symptoms during a manic episode. Agitation is a primary target of treatment. Changes in the Diagnostic and Statistical Manual of Mental Disorders (DSM) already reflect the tendency to move from a categorical approach to a dimensional approach. Whereas the DSM-IV classification differentiates manic, mixed, and depressive conditions (9), DSM-5 defines manic, manic with mixed features, depressive with mixed features, and depressive states (10).

A new and valid diagnostic tool for bipolar disorder is the Mini International Neuropsychiatric Interview (MINI) DSM-5 'with mixed features' specifier module. These are questions that the patients can answer themselves (Table) (11). The specifier indicates the presence of symptoms of the opposite pole. It is applicable to episodes of both depression and (hypo-) mania. The specifier module has been shown to be a valuable standardised tool for clinical and epidemiological research into bipolar disorder. There is good concurrent validity with psychiatrists' evaluations of DSM-5 mixed features in manic patients, with high detection of mixed features, and a low risk of over-diagnosis. This test can easily be incorporated into the routine psychiatric evaluation of patients with manic episodes.

Table: The new MINI patients' module for the DSM-5 'with mixed features' specifier (11)

Since you have been experiencing your current manic episode, have you almost every day had times when:			
Q1	You felt sad, empty, tearful, down, or depressed?	Y	N
Q2	a) You were less interested in most activities?	Y	N
	b) You had less pleasure doing the activities you used to enjoy?	Y	N
Q3	You were slowed down in your speech, thoughts or movements?	Y	N
Q4	a) You had fatigue?	Y	N
	b) You felt without energy?	Y	N
Q5	a) You had feelings of worthlessness?	Y	N
	b) You felt excessively guilty?	Y	N
Q6	You wished you were dead, considered hurting yourself, made plans to commit suicide or attempted suicide?	Y	N

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Strategies to develop novel therapies in HD: model systems and biomarkers

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The identification of potential targets for therapeutic intervention in Huntington's disease (HD) is a step-by-step process that requires an understanding of the pathomechanisms. CAG repeats in the huntingtin gene were shown to be the root cause of HD in 1993 (1). However, the development of efficient treatment options remains another challenge. As countless molecules, pathways and functions (e.g., neuronal signalling, axon growth, RNA transport, cellular energetics) are connected to the huntingtin gene, focusing on a single element in search for a target appears futile. The picture is rendered even more complicated by modifications at the molecular level, such as transcriptional activation, repression and demethylation, and changes of the numerous cell types over time. Another approach consists of candidate gene modifier studies. However, two decades of candidate studies have not yielded unequivocal, reproducible evidence for a genetic modifier. The CAG repeat expansion is unstable between generations (Figure), and it is also somatically unstable (2).

Drawing conclusions from transgenic models of HD is feasible, although these models hardly reflect the disease in humans in its entirety. Rather, their utility lies in modelling certain aspects of the disease. Other issues with transgenic models include overexpression artifacts and insertion-site/integration-site artifacts, genetic faithfulness (pure or interrupted CAG-repeat expansions), and regulation of transgene expression. Also, given that there are no established efficacious disease-modifying therapies for HD, the predictive value of "therapeutic findings" in HD models is currently unknown.

Based on the presence of kynurine pathway dysregulation in HD, genomic screening has implicated kynurenine 3-monooxygenase as a potential therapeutic target (3). Kynurine pathway metabolites have been shown to be dysregulated in HD patients (4). Inhibition of kynurenine 3-monooxygenase might be beneficial, through the modulation of synaptic pathways, prevention of neurodegeneration, and anti-inflammatory effects (5).

Moreover, suppression of the continuous production of mutant huntingtin gene products (gene silencing) is projected to reverse the HD phenotype (6). Both mRNA- and DNA-targeting agents are being developed. Reductions in huntingtin protein levels by decreasing mRNA translation are promoted by antisense oligonucleotides and small-interfering RNAs (7). However, these agents do not cross the blood–brain barrier, thus necessitating their direct CNS delivery (intraparenchymal or intrathecal administration; virus-assisted delivery; liposomal-/nanoparticle-assisted delivery). As all currently planned clinical trials will have only regional brain coverage, expectations with respect to self-evident clinical improvements need to be limited. In addition, the time it takes for lower huntingtin levels to translate into improved cellular and brain circuit functions, and finally into clinical improvements, is currently unknown. Biomarkers are required to demonstrate target engagement in relevant compartments and to map regional distribution. Nonetheless, large-scale targeted development of potential drugs for HD is on-going. Many additional potential targets that address numerous putative disease mechanisms are being evaluated (Table).

Registries like Enroll-HD will contribute to the clarification of some questions. Multiple clinical trials can be run in parallel, as potential participant numbers are no longer a limiting factor, and there are well-trained study sites on four continents. The goals of the research are the identification, validation and qualification of biomarkers, as well as the development and qualification of additional assessment tools in HD.

Table: Additional potential targets that address the putative disease mechanisms

• RNA misfolding/RNA splicing
• Protein misfolding/aggregate formation
• Huntingtin clearance (including interferon-beta)
• Excitotoxicity
• Neuroinflammation
• Mitochondrial function/metabolism/oxidative damage
• Exercise/cognitive training/biofeedback

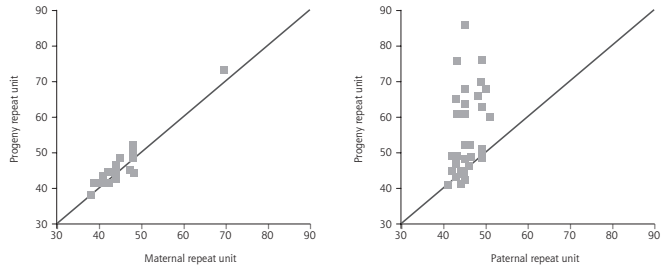

Figure: The CAG repeat expansion is intergenerationally unstable (x)

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Update on symptomatic and diseasemodifying treatments in HD

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In Huntington's disease (HD), several areas of mental and physical functioning are affected. At the psychiatric level, patients experience apathy, depression, irritability, and obsessive-compulsive disorder. Executive dysfunction and overt dementia are signs of cognitive deterioration, and the motor symptoms include chorea, dystonia, motor impersistence, gait disorder, and Parkinsonism. Non-pharmacological therapeutic measures can contribute to the maintenance of patient independence and quality of life, such as: speech therapy, occupational therapy, psychosocial counselling, nutrition, physical therapy, and surgery. Pharmacological interventions consist of neuroprotection on the one hand, and symptomatic treatment for both early and advanced disease, on the other.

A Cochrane review of 22 trials with a total of 1,254 patients evaluated symptomatic treatment of HD (1). Mostly, these studies assessed anti-dopaminergic drugs, glutamate receptor antagonists, and energy metabolites. Only tetrabenazine showed clear efficacy with regard to the control of chorea, while the remaining pharmacological interventions did not have consistent symptomatic control. The authors concluded that tetrabenazine is the anti-choreic drug with the best-quality data available. Another Cochrane review of eight trials that involved a total of 1,366 patients dealt with the effects on disease progression of vitamin E, idebenone, baclofen, lamotrigine, creatine, coenzyme Q10 plus remacemide, ethyl-eicosapentanoic acid, and riluzole (2). However, none of these trials produced positive results for the defined efficacy outcome measures, which prompted the conclusion that no pharmacological intervention has shown efficacy as a disease-modifying therapy for HD.

Various interventions that might change the disease phenotype and progression are currently in clinical development. Cysteamine, PBT2, creatine, and coenzyme Q10 are hypothesised to affect disease progression. Pridopidine, PDE10A, SD-809ER, deep brain stimulation, and transplantation are being tested with the goal of improving the motor syndrome.

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Case report

An unusual course of HD

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A male patient born in 1959 with a positive family history of Huntington's disease (HD) developed psychiatric symptoms in his early twenties (obsessive–compulsive disorder, depression, apathy, irritability, psychosis). This was followed by involuntary movements at the age of 31. At the age of 41, significant cognitive impairment set in. Two years later, genetic testing confirmed the clinical diagnosis of HD. Neuroimaging of the brain was performed in 2010 and revealed changes that are characteristic of a moderate stage of HD. Treatment was initiated for depression, motor symptoms and cognitive symptoms, but most measures were discontinued over time. At present, the patient only receives olanzapine.

The patient was entered into a database in 2007. Across seven years of observation, his performance according to several scales has hardly changed (i.e., motor symptoms, functional abilities and independence, cognitive capacity, behavioural disturbances, global clinical impression, quality of life according to SF-36). Amazingly, after 24 years of HD symptoms on top of several comorbidities and an unhealthy lifestyle (alcohol use, lonely life after divorce), the patient is still enthusiastic, active and able to lead an independent life. He has overcome all of his bad habits, such as his drinking and aggressive behaviour. Unexpected improvements, such as remission of depression, were not related to his treatment. In other family members (mainly women), the disease progression has been notably faster.

This benign HD course might be explained by male gender and other endogenous protective factors. Genome-wide association studies and epigenetic research might help to explain this phenomenon. In case of motor worsening in this patient, tetrabenazine will be considered, as an efficient treatment with minor interference with cognitive functions, so as to preserve the patient's independence.

Case report

Use of tetrabenazine for treatment-induced tardive dyskinesia – two cases

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A 46-year-old woman with a diagnosis of bipolar disorder was treated with depot perphenazine for several years due to manic episodes. When she developed tardive dyskinesia, the medication was changed first to aripiprazole and then to clozapine. At the time of introduction of tetrabenazine, she had had tardive dyskinesia for six years, and had received treatment with vitamin E, benzodiazepines, valproates and botulinum toxin injections. The patient's social and occupational functioning was significantly impaired.

Tetrabenazine therapy led to a reduction in her Abnormal Involuntary Movement Scale (AIMS) score from 18 to 4 points. She lost her involuntary movements in the upper limbs, and experienced significant reductions in her face-muscle dyskinesia. The treatment was well tolerated in doses of up to 75mg/day. Increased doses resulted in augmentation of dyskinetic movements and occurrence of extrapyramidal symptoms (tremor of the upper limbs, cog-wheel muscle tension, salivation). The improvement of her condition allowed the patient to return to her job.

Another female patient, aged 39 years, with a diagnosis of paranoid schizophrenia, developed tardive dyskinesia symptoms while on risperidone. The symptoms did not decrease in spite of treatment modification. With the application of tetrabenazine, the AIMS results showed a decrease from 23 points to 12 points in the fifth week of treatment. In week 9, at tetrabenazine 62.5mg/day, her AIMS score increased to 19 points. Doses of up to 75mg/day were well tolerated, but higher doses resulted in mood lowering, somnolence, apathy and loss of activity. Eventually, tetrabenazine had to be discontinued due to mental side effects.

Overall, it should be noted that high doses of tetrabenazine can produce extrapyramidal symptoms. As the second case shows, the mental state of a patient given tetrabenazine due to tardive dyskinesia should be stable; careful observation of the patient's mental and neurological condition is necessary.

Case report

Treatment of early-onset tardive dyskinesia

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A 61-year-old female was treated with risperidone because of depression, anxiety, agitation, vivid dreams, and insomnia. Mirtazapine was added because of adynamia, anhedonia, isolation, and lack of motivation. Only four months after the initiation of treatment, she experienced perioral dyskinesia and involuntary movements of the lower limbs. Risperidone was switched to tiaprid, and alprazolam and anticholinergics were added. Nevertheless, the patient developed pronounced tardive dyskinesia of the oro-bucco-linguo-masticatory muscles. Also, she displayed choreo-athetoid movements of the limbs at rest. Her gait was affected, but she did not experience falls. There were no other neurological symptoms. Computer tomography of the brain and electroencephalography did not yield any abnormalities.

The tiaprid treatment was tapered off, while the administration of mirtazapine and alprazolam was continued. Tetrabenazine 25mg/d was introduced. With these measures, the involuntary movements were significantly reduced, and the patient showed stable mood and normal behaviour.

There are only a few published cases of early-onset tardive dyskinesia (1,2). Treatment includes tetrabenazine, VMAT2 inhibitors (reserpine, methyldopa), ondansetron, donepezil, baclofen, pramipexole, clonidin, botulinum toxin, benzodiazepines (clonazepam) and vitamin B6. In males, a branched-chain amino-acid formula has been reported as beneficial. Deep brain stimulation can be useful. This case report shows that tardive dyskinesia can occur after short exposure to antipsychotic treatment. Therefore, serious consideration should be given to the indication, choice and dose of drug, and to treatment duration. Tetrabenzine is effective in the reduction of symptoms of tardive dyskinesia.

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