DRUG-INDUCED MOVEMENT DISORDERS

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The consequences of EPS

- Patient Distress
- Decreased QoL
- Poorer employment prospects
- Caregiver stress
EPS: effect on outcome

- Poor response
- Increased risk of relapse
- Prolonged hospitalisation
# Importance of EPS to patients

## Reasons for non-compliance

<table>
<thead>
<tr>
<th>Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side effects</td>
<td>35</td>
</tr>
<tr>
<td>Psychotic symptomatology</td>
<td>30</td>
</tr>
<tr>
<td>Denial of illness</td>
<td>21</td>
</tr>
<tr>
<td>Stated inefficacy</td>
<td>12</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Clinicians</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotic/idiosyncratic reasons</td>
<td>49</td>
</tr>
<tr>
<td>‘Transference’</td>
<td>11</td>
</tr>
<tr>
<td>Side effects</td>
<td>7</td>
</tr>
</tbody>
</table>

Hoge et al 1990
NEUROLEPTIC-INDUCED MOVEMENT DISORDERS

- **Acute:**
  - Parkinsonian symptoms
  - Acute dystonia
  - Akathisia
  - NMS

- **Tardive:**
  - Dyskinesia, dystonia, akathisia, tics, tremor, parkinsonism
PARKINSONIAN SIDE EFFECTS

- Rigidity
- Tremor
- Bradykinesia
- Gait/posture abnormality
Comparing atypical to standard agents in terms of EPS

- Atypical agents are associated with significantly less EPS than standard agents.

- Several (efficacy and side-effect) benefits accrue from EPS advantage, eg individualisation of dose, quality of life.

- The essence of atypicality is low EPS.
Comparing different atypical antipsychotics in terms of EPS

- Both pharmacological studies and clinical trials indicate that atypical antipsychotics differ in propensity to cause EPS.
- Seroquel and clozapine show no dose-related increase in EPS.
- In contrast, at higher doses, olanzapine and risperidone cause greater incidence of EPS than placebo.
Striatal D$_2$ receptor occupancy rates

Kasper et al. 1999

<table>
<thead>
<tr>
<th>Drug</th>
<th>D$_2$ receptor occupancy rate (%)</th>
<th>n value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol 13 mg</td>
<td>88</td>
<td>6</td>
</tr>
<tr>
<td>Risperidone 8 mg</td>
<td>75</td>
<td>6</td>
</tr>
<tr>
<td>Olanzapine 18 mg</td>
<td>73</td>
<td>6</td>
</tr>
<tr>
<td>Zotepine 225 mg</td>
<td>73</td>
<td>12</td>
</tr>
<tr>
<td>Risperidone 3 mg</td>
<td>64</td>
<td>5</td>
</tr>
<tr>
<td>Sertindole 19 mg</td>
<td>61</td>
<td>8</td>
</tr>
<tr>
<td>Seroquel 600 mg</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Clozapine 475 mg</td>
<td>26</td>
<td>4</td>
</tr>
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</table>

Kasper et al. 1999
## Striatal $D_2$ and $5HT_{2A}$ Receptor Occupancy Rates

Kasper et al. 1999

<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
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<tbody>
<tr>
<td>Low</td>
<td></td>
<td>Haloperidol</td>
</tr>
<tr>
<td>High</td>
<td>Clozapine</td>
<td>Olanzapine</td>
</tr>
<tr>
<td></td>
<td>Seroquel</td>
<td>Risperidone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sertindole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ziprasidone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zotepine</td>
</tr>
</tbody>
</table>
Relation of Threshold for Clinical Response to Occupancy of Dopamine D₂ and Serotonin 5-HT₂ Receptors for Haloperidol, Olanzapine, and Risperidone


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\(^a\) Threshold for response to haloperidol is 65% (1.5–2.1 mg/day).

\(^b\) Olanzapine (7.5–10 mg/day) and risperidone (2 mg/day) also reach their thresholds of effectiveness only when their D₂ occupancy reaches 65%, despite the fact that haloperidol has a negligible effect at the 5-HT₂ receptor and olanzapine and risperidone show high 5-HT₂ occupancy (29, 30, 35).
Dose-response curve for antipsychotic and EPS effects for neuroleptics and ‘atypical’ antipsychotics

*Normalised for all antipsychotics

Adapted from Jibson & Tandon 1998
Risperidone: EPS are dose-related

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Risperidone (n=229)</th>
<th>Haloperidol (n=227)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>16</td>
<td>4</td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05 vs 1 or 4 mg/day risperidone
** p<0.05 vs 1, 4, 8 or 12 mg/day risperidone

Owens 1994, Peuskens 1995
Olanzapine: EPS are dose-related

Differences in treatment-emergent EPS compared to placebo seen at dosages commonly used in clinical practice

* statistically significantly different from placebo

Olanzapine US Prescribing Information 1999
Ziprasidone and EPS

% patients

- Akathisia
- Use of anticholinergics

Ziprasidone dosage (mg/d)

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Placebo (n=92)</th>
<th>80 (n=106)</th>
<th>160 (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Daniel et al 1999, p=NS
Seroquel: Lack of EPS at all doses

% patients

Seroquel dosage (mg/d)

- Placebo: n=51
- 75 mg: n=53
- 150 mg: n=48
- 300 mg: n=52
- 600 mg: n=51
- 750 mg: n=54

Medication for EPS
Total EPS events

p=NS

AstraZeneca: Data on file
EPS in the elderly

- Present in >50% of elderly patients receiving standard antipsychotics
- Incidence increases with years of exposure
- Elderly are most susceptible to akathisia, pseudoparkinsonism and TD
- EPS and especially TD are more persistent in elderly than in the young
- Emergence of EPS at low doses limits treatment choices
- Therapies for EPS, eg, anticholinergics, beta-blockers, may be poorly tolerated
ACUTE DYSTONIA
Akathisia
Discriminating features of acute akathisia
(Sachdev & Kruk, 1994)

- Shifting weight from foot to foot or walking on one spot
- Inability to keep legs still (subjectively)
- Feelings of inner restlessness
- Shifting of body position in chair
Disorders with subjective distress

- Psychotic agitation
- Anxiety
- Non-akathisia neuroleptic dysphoria
- Agitated depression
- Drug withdrawal
- The ‘jitteriness’ syndrome
- Restless legs syndrome
- Hysteria and malingering
DIFFERENTIAL DIAGNOSIS -2

- Disorders with motor features without subjective distress
  - Stereotypies and mannerisms
  - Tremors
  - Drug-induced dyskinesia
  - Myoclonus
  - Other movement disorders: tics, Huntington’s, Wilson’s, etc.
  - Endocrine/metabolic disorders: hyperthyroidism, hypoparathyroidism
Idiopathic RLS (Ekbom’s syndrome)

- Sensory symptoms, usually in the legs, aggravated by rest and worse at nightfall
- Motor restlessness in response to sensory symptoms
- Dyskinesia, presenting as myoclonic-like jerks during waking hours or as PLMS
- A normal neurological examination
Investigation of a patient with RLS to rule out other causes

- Drug and alcohol history
- History of metabolic and neurological disorders
- History of pregnancy
- Detailed physical examination
- Laboratory investigations
  - Haematological parameters
  - Serum iron status
  - Serum folate
  - urea/creatinine/fastig blood glucose
  - ESR, rheumatoid factor
  - NCV/EMG/ nerve and muscle biopsy
Proposed model for the development of acute neuroleptic-induced akathisia indicating its risk factors.

Data from Sachdev and Kruk (1993)
Patients treated with a neuroleptic drug

Development of symptoms of acute akathisia

Management

Establish the diagnosis (repeat assessment and observation)

Other disorder excluded

Is the causative drug still needed?

Reduce dosage

Yes

Discontinue drug, change to another antipsychotic or a non-antipsychotic

Has akathisia remitted?

Treatment

yes

Leave algorithm

First-line

Anticholinergic or β-blocker (sequentially or together)

Serotonin a antagonist (ritanserin or mianserin)

Second-line

Benazodiazepines

Has treatment been effective?

yes

Leave algorithm

Third-line

Try miscellaneous drugs [amantadine, clonidine, amitriptyline, valproic acid, nicotine patches]

Algorithm for the management and treatment of neuroleptic-induced acute akathisia (adapted from Sachdev, 2000)
THE CURRENT STATUS OF TARDIVE DYSKINESIA

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School of Psychiatry
University of New South Wales

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- **Tardive** = delayed onset
- **Dyskinesia** = abnormal movement
  - choreiform
  - athetoid
  - dystonic
  - stereotypic
  - combination of the above

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Neuroleptic-induced tardive sub-syndromes

MOVEMENT DISORDERS:
- Tardive dyskinesia (TD)
  - Oro-buccal-lingual-facial (OBLF) syndrome
  - Limb-truncal (LT) syndrome
  - Mixed
- Tardive akathisia (TA)
- Tardive dystonia (TDt)
- Tardive tics and Tourette's (TTS)
- Tardive myoclonus (TMyo)
- Tardive tremor (TTrem)
- Tardive parkinsonism (TPark)

BEHAVIOURAL SYNDROMES:
- Supersensitivity psychosis (SP)
- Tardive dysmentia (TDem)
- Tardive dysbehaviour (TBeh)
DSM-IV RESEARCH DIAGNOSTIC CRITERIA FOR TARDIVE DYSKINESIA

- Involuntary movements of tongue, jaw, trunk or extremities in relation to neuroleptic medication.
- Movements present for at least 4 weeks, and have any of the following patterns:
  - Choreiform (rapid, jerky, nonrepetitive)
  - Athetoid (slow, sinuous, continual)
  - Rhythmic (stereotypies)
- Develop during exposure to neuroleptics or within 4 weeks of withdrawal of oral (or 8 weeks of depot) neuroleptic.
- Exposure of at least 3 months of neuroleptic (1 month if >60 years old)
- Symptoms not due to a neurologic or general medical condition, ill-fitting dentures, or other medication.
- Symptoms not accounted for by an acute movement disorder.

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TERMINOLOGY

- Definite / Probable TD
- Transient / Persistent TD
- Masked / Covert TD
- Withdrawal Emergent TD
THE MOVEMENTS OF TD

- The OBLF musculature is most commonly affected, but any other striated muscle may be affected.
- Vermicular movements of tongue sitting in the base of the mouth are an early and common feature.
- The movements fluctuate over time, increase with emotional arousal and during distracting tasks, decrease with relaxation and when involved muscle being used, and disappear during sleep.
- Poor dental status may worsen oral-lingual movements.
- In mild cases, patient may be unaware of movements (issue of insight).
- They show a variable response to neuroleptics and their withdrawal.

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PREVALENCE

- Reported prevalence ranges from 3 to 62%
- Mean prevalence 24%
- Prevalence affected by:
  - Populations studied
  - Institutional/non-institutional
  - Medication status
  - Age group
  - Methodological issues

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## INCIDENCE STUDIES

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Years</th>
<th>Risk/year</th>
<th>5-year risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibson, 1981</td>
<td>343</td>
<td>3</td>
<td>5.6%</td>
<td>24.4%</td>
</tr>
<tr>
<td>Kane et al, 1982</td>
<td>554</td>
<td>7</td>
<td>3.9%</td>
<td>17.8%</td>
</tr>
<tr>
<td>Yassa &amp; Nair, 1984</td>
<td>108</td>
<td>2</td>
<td>3.9%</td>
<td>17.5%</td>
</tr>
<tr>
<td>Chouinard et al, 1986</td>
<td>131</td>
<td>5</td>
<td>8.7%</td>
<td>35.1%</td>
</tr>
<tr>
<td>Morgenstern, 1993</td>
<td>398</td>
<td>5</td>
<td>5.3%</td>
<td>20%</td>
</tr>
<tr>
<td>Jeste et al, 1995(^1)</td>
<td>266</td>
<td>3</td>
<td>20%</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Chakos et al, 1996(^2)</td>
<td>118</td>
<td>4</td>
<td>5.2%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Caligiuri et al, 1997(^a)</td>
<td>378</td>
<td>3</td>
<td>7.6%</td>
<td>22.9%</td>
</tr>
<tr>
<td>Woerner et al, 1998(^1)</td>
<td>261</td>
<td>3</td>
<td>17.6%</td>
<td>53%(^1)</td>
</tr>
</tbody>
</table>

1 Elderly neuropsychiatric patients;
2 First-onset schizophrenic patients followed up
\(^a\) Severe tardive dyskinesia only
Tardive dyskinesia: increased risk in elderly

% patients with TD

Mean age 65.5 years
n=266

Mean age 29 years
n=850

Cumulative years of treatment

Jeste et al 1995

Kane 1995
RISK FACTORS - I

- **Age**
  - Manifold increase in incidence
  - Greater severity
  - Greater persistence

- **Gender**
  - Female preponderance (1.69:1)
  - Inconsistent studies

- **Interaction of age and gender**
RISK FACTORS - II

Psychiatric diagnosis

- Schizophrenia, esp with negative symptoms
- Affective disorders
- Mental retardation
- Organic brain dysfunction
Drug-treatment variables

- Neuroleptics:
  - Duration of use
  - Drug dose
  - Drug type
    - High v. low-potency
    - Typical v. atypical
  - Age at initiation of dose
  - Drug holidays
  - H/O acute EPSE or akathisia
  - Anticholinergic drugs
  - Lithium
  - SSRI and TC antidepressants
Mean Rate of Tardive Dyskenesia (%)

- Total (N=2,769, 11 studies)
- Children (N=77, one study)
- Adult Patients (N=1,964, six studies)
- Adults and Elderly Patients (N=207, one study)
- Elderly Patients (N=521, four studies)
- Haloperidol-Treated Patients (N=408, three studies)

Subjects Treated With Second-Generation Antipsychotics
TD rates from 12 trials 2004-07

Incidence Prevalence

FGA 7.70% 32.40%
SGA 2.98% 13.10%

Correll & Schenk, 2008
RISK FACTORS - III

Drug-treatment variables

- Neuroleptics:
  - Duration of use
  - Drug dose
  - Drug type
    - High v. low-potency
    - Typical v. atypical
  - Age at initiation of dose
- Drug holidays
- H/O acute EPSE or akathisia
  - Anticholinergic drugs
  - Lithium
  - SSRI and TC antidepressants
RISK FACTORS - IV

HOST-RELATED VARIABLES

- Smoking
- Diabetes mellitus
- Alcohol abuse/dependence
- Dental status
  - Ill-fitting dentures
  - Edentulous status
- Ethnicity
- Familial-genetic factors
  - Carriers of mutated CYP2D6 gene
  - D3 receptor gene variant
NATURAL HISTORY

- A fluctuating course with spontaneous remissions and exacerbations.
- Longer-term studies more favourable in prognosis, with about 50% showing 50% improvement from 5 to 10 years.
- Prognosis most favourable if drug can be stopped.
- Prognosis better for withdrawal-emergent dyskinesia: 3/4 improve over 3 months
DIFFERENTIAL DIAGNOSIS

- **Acute dyskinesias**
  - neuroleptic-induced
  - rabbit syndrome

- **Dyskinesias due to other drugs**
  - anticonvulsants (phenytoin, carbamazepine)
  - oral contraceptives
  - stimulants
  - dopamine agonists (L-dopa, bromocriptine)
  - lithium
  - tricyclic antidepressants, SSRIs
  - anticholinergics, antihistaminics

  “True tardive dyskinesias may occur with L-dopa, stimulants, DA antagonists not used as antipsychotics, SSRIs, TCs (?), anticholinergics and antihistaminics”

- **Secondary to neurological/systemic disease:**
  Huntington’s, Wilson’s, Sydenham’s chorea, Tourette’s, basal ganglia infarcts and tumours, autoimmune diseases (SLE, antiphospholipid syndrome), endocrine disorders (hyperthyroidism and hypoparathyroidism)
DIFFERENTIAL DIAGNOSIS - II

- **Spontaneous dyskinesias:**
  - 0.8%, 6.0% and 7.8% in the 6th, 7th and 8th decades of life (Klawans & Barr, 1982)
  - 4% in healthy elderly (mean age 73 years) (Kane et al, 1982)
  - Rates higher in psychogeriatric patients, especially dementia
  - Rates higher if ill-fitting dentures

- **Dyskinesias in schizophrenia:**
  - Kraepelin reported “peculiar, irregular, choreiform, outspreading movements”
  - Rates vary from nil to as high as 53% (Owens et al, 1982) in never-treated cases
  - Increased prevalence with age and severity
  - Some studies in first-episode cases:
    - 1% (Chatterjee et al, 1995)
    - 7.6% (Gevins et al, 1998)
    - 7% (Puri et al, 1999)
  - Never treated chronic inpatients:
    - 29% (McCreadie et al, 1982, UK)
    - 29% (McCreadie et al, 1996, India)
    - 53% (Owens et al, 1982, UK)
    - 28% (Fenton et al, 1994, USA)
    - 27% (Hoffman et al, 1996, Morocco)
    - 0 (McCreadie & Ohaeri, 1994, Nigeria)
LABORATORY INVESTIGATIONS

- FBC (polycythaemia vera and other disorders)
- Serum electrolytes (Na, Ca, P metabolism abnormalities)
- LFTs (Wilson's disease, etc.)
- TFTs (hyperthyroidism)
- Serum Cu and ceruloplasmin and, if necessary, urinary Cu and AAs (Wilson's)
- Connective tissue disease screen (SLE, other vasculitides)
- Head CT or MRI (Huntington's disease, brain tumour, CVA, Fahr's syndrome, etc.)
RATING METHODS

- Multi-item rating scales, e.g. AIMS
- Videotape ratings
- Instrumental ratings:
  - Electromechanical instruments
  - Frequency counts
  - Ultrasound
  - Accelerometers
  - Vocal assessment
  - EMG
# Abnormal Involuntary Movement Scale

<table>
<thead>
<tr>
<th>Body region</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniofacial</td>
<td></td>
</tr>
<tr>
<td>Facial &amp; eye</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Perioral</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Lingual</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Jaw</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Upper limbs and trunk</td>
<td></td>
</tr>
<tr>
<td>Hands and arms</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Trunk</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Lower limbs</td>
<td></td>
</tr>
<tr>
<td>Legs and feet</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Overall rating of severity</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Severity of disability due to dyskinesia</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Dental status:</td>
<td></td>
</tr>
<tr>
<td>Problems with teeth</td>
<td>0 1</td>
</tr>
<tr>
<td>Patient wears dentures</td>
<td>0 1</td>
</tr>
</tbody>
</table>
Neurotransmitter/receptor dysfunction
- **Dopamine supersensitivity hypothesis**
- D1/D2 interaction
- Noradrenergic hypothesis
- Cholinergic hypothesis
- GABAergic hypothesis

Neuronal degeneration hypothesis (Striatal GABA neurons or cholinergic interneurons)
- Free radical mechanisms
- Excitotoxicity
Nigrostriatal pathway

Mesolimbic pathway

- dopamine
- typical neuroleptic
- atypical neuroleptic
- D2 receptor – nigrostriatal pathway
- D2 receptor – mesolimbic pathway
DOPAMINERGIC SUPERSENSITIVITY HYPOTHESIS

PREDICTIONS

- Chronic neuroleptics produce DA supersensitivity
- DA supersensitivity persists after DA withdrawal
- DA supersensitivity correlates with behavioural expression in animals
- DA antagonists reduce TD symptoms
- Presynaptic DA depleters reduce DA symptoms
- DA agonists increase TD symptoms
  - Direct agonists
  - Indirect agonists
- TD patients have increased DA receptors in brain
- TD patients have lower HVA levels
- TD patients have greater neuroendocrine response to DA agonists
PATHOPHYSIOLOGY

Neurotransmitter/receptor dysfunction
- Dopamine supersensitivity hypothesis
- D1/D2 interaction
- Noradrenergic hypothesis
- Cholinergic hypothesis
- GABAergic hypothesis

Neuronal degeneration hypothesis (Striatal GABA neurons or cholinergic interneurons)
- Free radical mechanisms
- Excitotoxicity
Neuroleptic drugs

DA blockade

Substratum of vulnerability (Negative Schiz, Affective Disorders, Aging, Diabetes, Smoking)

DA receptor supersensitivity

GABA activity

Tardive dyskinesia

DA blockade

GABA activity

Apoptosis & Neuronal Death (esp. GABA neurones)

DA turnover

free radical production

metal deposition (esp. Fe, Mn) in basal ganglia

Oxidative stress....

Figure: Pathogenetic mechanisms for tardive dyskinesia

(DA dopamine; GABA gamma amino butyric acid; Fe iron; Mn manganese)
Does clozapine cause tardive dyskinesia?
TREATMENT

- There is no consistently effective therapy
- Prevention is the best strategy
STRATEGIES FOR PREVENTION

- Restrict the long-term use of neuroleptics to well-defined indications
- Use non-neuroleptic drugs for agitation, insomnia, anxiety etc.
- Use neuroleptics at the lowest effective doses for the shortest time
- The use of atypical neuroleptics (as first line)
- Address some risk factors (smoking, dental status, alcohol use, diabetes, anticholinergic medication)
- Evaluate patients at regular intervals for early diagnosis
- Education of patient and informed consent
MANAGEMENT

- Minimise neuroleptic exposure
  - Withdraw if possible
  - Use minimal effective dose
  - Use alternatives, eg lithium, carbamazepine, valproate, benzodiazepines, etc.
- Use atypical neuroleptics
- Withdraw anticholinergic drugs
- Attend to dentition and dental hygiene
- Education of patient and concerned others, and informed consent
TREATMENT STRATEGY

- It is difficult to predict an individual’s response to a particular drug.
- It is advisable to have a systematic plan of management in which the order of drugs to be tried is clearly stated.
Dopaminergic

- **Antagonists:**
  - Classical neuroleptics
  - Catecholamine depleters
    - Tetrabenazine, reserpine, oxypertine
  - Atypical neuroleptics
    - Clozapine, risperidone, olanzapine
  - Other catecholamine depleters
    - AMPT

- **Agonists:**
  - Bromocriptine, L-dopa, apomorphine, piribedil, amphetamine
  - L-deprenyl
THERAPEUTIC AGENTS - II

- **NORADRENERGIC ANTAGONISTS**
  - Propranolol, clonidine

- **CHOLINERGIC DRUGS**
  - Physostigmine
  - Deanol, choline, lecithin

- **GABA-ERGIC DRUGS**
  - Benzodiazepines, valproate, gamma-vinyl GABA, baclofen

- **SEROTONERGIC DRUGS**
  - L-tryptophan, 5-HTP, cyproheptadine

- **OTHER**
  - Lithium carbonate
  - Ca channel antagonists
    - Verapamil, diltiazem, nifedipine

P.Sachdev@unsw.edu.au
ANTI-OXIDANTS

- **Vit E:**
  - Of 11 studies, 9 demonstrated benefit in established cases of TD
  - Most studies short-term
  - Two long-term studies:
    - Adler et al 1998: 1600 IU for 8 months +ve
    - VA Co-op Study: 158 subjects over 1 year -ve
  
  “Vit E not proven to be effective in general”

- **Other anti-oxidants:** e.g. L-deprenyl
Figure 1. Selegeline.

Mean total mouth movements over different test occasions for SEL-CON, SEL-FLU, FLU, and CON groups.
HEROIC MEASURES

- Botulinum toxin
- Neurosurgery (pallidotomy)
- Deep brain stimulation
**TARDIVE AKATHISIA**

**BEST DISCRIMINATING FEATURES**

(Sachdev, 1995)

- Semipurposeful leg/foot movements while sitting
- Inability to remain still, subjectively
- Purposeless foot movements while standing
- Purposeless hand/arm movements
- Shifting body position in a chair while sitting
Patient receiving long term treatment with an antipsychotic drugs

Development of symptoms of tardive akathisia

Management

Establish the diagnosis (repeat assessment and observation)

Other disorder excluded

Is the causative drug still needed?

Yes

Reduce dosage

Has akathisia remitted?

Yes

Leave algorithm

No

Discontinue drug, change to another antipsychotic or a non antipsychotic

Do not treat

Is akathisia severe?

No

First-line

Catecholamine depleter e.g. tetrabenazine

Second-line

Anticholinergic

β-Blocker

Yes

Leave algorithm

No

Has treatment been effective?

Third-line

Try miscellaneous drugs [clozapine, clonidine, benzodiazepines, opioids, valproic acid (sodium valproate)]

Antioxidant therapy (e.g. vit E)

Fig. 3. Algorithm for the management and treatment of neuroleptic-induced acute akathisia (adapted from Sachdev, 2000)
Treatment of tardive dystonia

- **Focal or segmental dystonia:**
  - Botulinum toxin

- **Generalized dystonia:**
  - Anticholinergic drug
  - Tetrabenazine
  - Baclofen (intrathecal for axial dystonia)
  - Neuroleptics (?) – clozapine, olanzapine, quetiapine, sulpiride

- **Surgical:**
  - Pallidotomy
  - Bilateral DBS
  - Thalamotomy
NEUROLEPTIC MALIGNANT SYNDROME

PERMINDER SACHDEV
UNIVERSITY OF NEW SOUTH WALES
NEUROPSYCHIATRIC INSTITUTE,
THE PRINCE OF WALES HOSPITALS,
SYDNEY
Neuroleptic malignant syndrome

- First described by Delay in 1960

- Categorical Versus Dimensional
  - Spectrum of neuroleptic sensitivity

- Sensitivity, specificity and reliability of existing criteria

- Relationship to similar syndromes
  - malignant hyperthermia
  - lethal catatonia
  - serotonin syndrome
EPIDEMIOLOGY

- Rare? <1% of neuroleptic exposures
- Incidence ranges from 0.01% to 2% in different studies
- Prospective studies
  - Keck et al, 1987 0.9%
  - Friedman et al, 1988 0.2%
  - Gelenberg et al, 1988 0.07%
- Male: Female 2:1 (?)
- Higher in young patients (range 1-92 years)
Clinical features of NMS

- **Hyperthermia**
- **Muscle rigidity**
- **Autonomic dysfunction**
  - Respiratory / cardiovascular
  - Other - diaphoresis, incontinence, dysuria, pallor
- **Altered mental state**
  - agitation, lethargy, muteness, confusion, stupor
- **Movement disorders**
  - bradykinesia, tremor, dystonia, chorea, myoclonus
- **Other neurological:**
  - seizures, ataxia, nystagmus, gaze paresis, reflex changes
Laboratory features of NMS

- Elevated creatine kinase
- Polymorphonuclear leukocytosis
- elevated APase, LDH, ALT, AST
- Hypocalcemia
- Hypomagnesemia
- Hypoferremia
- Proteinuria
- Myoglobinuria
NMS Criteria: DSM IV

- Muscle rigidity & fever associated with neuroleptics
- 2 or more of:
  - diaphoresis, dysphagia, tremor, incontinence, altered level of consciousness, mutism, ↑ HR, labile BP, ↑ WCC, ↑ CK
NMS Criteria: Pope

1. Fever > 38°C
2. Severe EPSE
   - cogwheeling, lead pipe, chorea, dyskinesia, posturing
3. Autonomic Dysfunction
   - 2 or more of ↑ BP, ↑ HR, ↑ RR, diaph, incont

Definite = 1+2+3

Probable = 2 of above +1 of altered consciousness, ↑ WCC, ↑ CK
NMS Criteria: Caroff

1. Neuroleptic exposure
2. Temperature
3. Muscle rigidity
4. Five of:
   - altered consciousness, ↑ HR, ↑ or ↓ BP, ↑ RR or hypoxia, diaphoresis, sialorrhoea, tremor, incontinence, ↑ CK or myoglobinuria, ↑ WCC, acidosis
NMS Criteria: Levenson

- **Major:**
  - Fever, Rigidity, ↑ CK
- **Minor:**
  - ↑ HR, ↑ or ↓ BP, ↑ RR, diaphoresis, ↑ WCC, altered consciousness

- **3 Major or 2 Major + 4 minor = High Probability**
Table 1. Published Criteria Sets for NMS

<table>
<thead>
<tr>
<th></th>
<th>Caroff et al.(^a)</th>
<th>Levenson et al.(^b)</th>
<th>Pope et al.(^c)</th>
<th>DSM-IV-TR(^d)</th>
<th>Adityanjee et al.(^e)</th>
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<tbody>
<tr>
<td>Rigidity</td>
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<td>+</td>
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<tr>
<td>Tachycardia</td>
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<td>Festinating gait</td>
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<td>Flexor-extensor posturing</td>
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From: Pandya & Pozuelo 2004
Results of first factor analysis ($n = 25$)

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<th>Cluster</th>
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<tr>
<td>I</td>
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<tr>
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<td>Posturing</td>
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<tr>
<td></td>
<td>Leucocytosis</td>
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<tr>
<td>II</td>
<td>Systolic BP</td>
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<td>Diastolic BP</td>
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<td>Incontinence</td>
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<td>III</td>
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<td>Waxy flexibility</td>
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<td>Mutism</td>
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<td>IV</td>
<td>Temperature</td>
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<td>Diaphoresis</td>
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<td>Resting tremor</td>
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<td>V</td>
<td>Extrapyramidal rigidity</td>
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<td></td>
<td>Dystonia</td>
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<tr>
<td>VI</td>
<td>Level of consciousness</td>
</tr>
</tbody>
</table>

![Factor Scree Plot](image)

Fig. 1. Factor scree plot showing the variance explained by each factor. Factors with eigenvalue >1 are included. The cumulative percentage of variance is indicated above the mark for each factor.

Sachdev PS. Psychiatry Res 2005; 135:249-256
NMS Criteria: Sachdev

A. Recent use of DA antagonist or withdrawal of DA agonist

B. Presence of fever (≥37.5°C) and 2 or more of following:
   1. Altered consciousness
   2. Severe extrapyramidal rigidity or catatonia
   3. Autonomic dysfunction

C. Presence of at least one of:
   1. Raised CPK
   2. Raised WBC count
   3. Extrapyramidal signs if not included in B

D. Develops over 24-72 hours

E. The symptoms, signs and lab features cannot be accounted for by another known aetiology.
### NMS Rating Scale

**Patient’s Name:** ________________________________  **Date:** __________________

**Rater:** ________________________________  **Time of rating:** _____ am/pm

**Rating performed:** For whole day/one time point

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<th>2</th>
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<th><strong>Sub-total</strong></th>
<th><strong>Score</strong></th>
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</tbody>
</table>

Sum total _____/36
CAUSES OF NMS -1

- Psychiatric patients
  - First exposure to neuroleptics
  - Re-exposure to neuroleptics
  - Increase in neuroleptic dose or potency
  - Dehydration /metabolic disturbance in stably medicated patient
  - Sudden withdrawal of amantadine
  - Treatment with lithium (?)
  - Withdrawal of anticholinergics
  - Antidepressants: clomipramine, venlafaxine
CAUSES OF NMS -2

- Neurological patients
  - Huntington’s or Tourette’s patients treated with neuroleptics
  - Dementia patients treated with neuroleptics
  - Parkinson’s disease
    - Sudden withdrawal of dopaminergic drug
    - “Off” period
    - “On-Off” treated with lithium
CAUSES OF NMS -3

- Nonpsychiatric, non-neurological patients
  - Treated with neuroleptic for sedation
  - Treated with metoclopramide
  - Cocaine abuse
Which neuroleptic?

- Are atypicals less likely to cause NMS?
  - Reports with all newer antipsychotics

- Is clozapine safe?
  - Risk similar to classic neuroleptics (Sachdev et al, 1995)
  - Syndrome may be atypical

- Is aripiprazole safe?
  - Recent case reports
NMS: Potential Risk Factors

- **Medication Factors**
  - Newly exposed, dose, rate of escalation, route (Viejo et al 2003; Sachdev et al 1997)
  - Potency, concomitant Li or anticholinergics, withdrawal of anticholinergics or dopamine agonists.

- **Patient factors**

- **Pre-existing brain disease** (Caroff 1980, Shalev et al 1986)
  - MR (Viejo et al 2003), PD.

- **High ambient temperature** (Shalev 1988), Prior NMS, Post Partum (Fido ‘99).
NMS: Pathophysiology
Dopamine Hypothesis

- Hypothalamic blockade → impaired temp regulation
- Nigrostriatal blockade → muscle rigidity
- Diencephalospinal blockade → autonomic dysfunction & muscle rigidity
- Reticular activating system → change in consciousness
<table>
<thead>
<tr>
<th>Line of Evidence</th>
<th>For</th>
<th>Against</th>
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</thead>
<tbody>
<tr>
<td>Causative agents: functional dopamine depletors</td>
<td>Association with neuroleptics (NB: potency &amp; dose), tetrabenazine, withdrawal of L-Dopa, bromocriptine, etc.</td>
<td>NMS observed with neuroleptics withdrawal and with &quot;novel&quot; antipsychotics</td>
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<tr>
<td>Treatments</td>
<td>Aim to reverse the functional dopamine depletion (ECT, Bromocriptine, Amantadine)</td>
<td>Efficacy of Rx not proven/ other Rx</td>
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<td>Pathophysiology</td>
<td>CSF: low HVA</td>
<td>CSF: low 5HIAA, high NE</td>
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<td>PM: low striatal D &amp; HVA</td>
<td>PM: low hypothal. NE</td>
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<td>hyperthermic effects in rats on D blockers when given D releasing agents</td>
<td>Urine: high Catechol</td>
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<tr>
<td>Animal Models</td>
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<td>effects blocked by 5HT antagonents</td>
</tr>
<tr>
<td>Functional Imaging</td>
<td>basal ganglia abn</td>
<td>findings non-specific</td>
</tr>
</tbody>
</table>
Striatal $D_2$ receptor occupancy rates

- Haloperidol 13 mg, n=6, 88%
- Risperidone 8 mg, n=6, 75%
- Olanzapine 18 mg, n=6, 73%
- Zotepine 225 mg, n=12, 73%
- Risperidone 3 mg, n=5, 64%
- Sertindole 19 mg, n=8, 61%
- Seroquel 600 mg, n=3, 26%
- Clozapine 475 mg, n=4, 26%

$D_2$ receptor occupancy rate (%)

Kasper et al 1999
Neuroleptic malignant syndrome
Differential diagnosis

- lethal catatonia
- serotonin syndrome
- malignant syndrome of PD
- heat stroke (no rigidity)
- encephalitis (consider LP)
- CNS mass lesions
- lithium toxicity
- monoamine oxidase inhibitor overdose
- strychnine poisoning
Lethal catatonia

- Historical reports of Bell's mania (1849) and lethal catatonia (1934) predate neuroleptics
- Literature does not clearly distinguish from neuroleptic malignant syndrome, catatonia due to a medical condition or a functional catatonia complicated by medical illness.
- Several authors have reported on a residual catatonia arising after the resolution of the more severe manifestations of NMS.
- Castillo (1989) suggests clear differentiation from NMS via:
  - onset with a prodrome of 2-8 weeks
  - initially excitement, restlessness or anxiety, psychosis and acrocyanosis
  - eventually: violence, chorea, refusal to eat or drink, cachexia, seizures
- Much disputed
## Triad of Clinical Features of Serotonin Syndrome Seen in Humans

<table>
<thead>
<tr>
<th>Neuromuscular Effects</th>
<th>Autonomic Effects</th>
<th>Mental Status Changes</th>
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</thead>
<tbody>
<tr>
<td>Hyperreflexia</td>
<td>Hyperthermia: mild, &lt;38.5°C; severe, &gt;38.5°C</td>
<td>Agitation, Hypomania, Anxiety, Confusion</td>
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<tr>
<td>Clonus</td>
<td>Tachycardia</td>
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<tr>
<td>Ocular clonus</td>
<td>Diaphoresis</td>
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<td>Myoclonus</td>
<td>Flushing</td>
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<td>Shivering</td>
<td>Mydriasis</td>
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<td>Tremor</td>
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<tr>
<td>Hypertonia/rigidity</td>
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</tr>
</tbody>
</table>

Clinical Findings Associated With Malignant Hyperthermia

Clinical Signs
Unexplained increase in end-tidal CO2 during general anesthesia
Markedly increased minute ventilation during spontaneous ventilation
Tachycardia, hypertension
Skin mottling
Generalized muscle rigidity, masseter muscle spasm, or both†
Hyperthermia‡
Hyperkalemia-induced arrhythmias: premature ventricular contractions, ventricular tachycardia, ventricular fibrillation
Cola-colored urine (evidence of myoglobinuria)
Disseminated intravascular coagulation

Laboratory Findings
Increased PaCO2
Metabolic (lactic) acidosis
Evidence of rhabdomyolysis: hyperkalemia, increased plasma creatine kinase, and myoglobin in blood and urine
Abnormal coagulation tests
The pathophysiology of acute malignant hyperthermia

Litman & Rosenberg
JAMA, June 15, 2005—Vol 293, No. 23
<table>
<thead>
<tr>
<th>Hyperthermic syndrome</th>
<th>Causative drugs</th>
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<tbody>
<tr>
<td>Malignant hyperthermia</td>
<td><strong>Anesthetic gases:</strong> halothane, enflurane, isoflurane, methoxyflurane, cyclopropane, diethyl ether, ethylene</td>
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<td></td>
<td><strong>Muscle relaxers:</strong> succinylcholine, decamethonium, gallamine</td>
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<td></td>
<td><strong>Neuroleptics:</strong> phenothiazines, butyrophenones, thioxanthenes</td>
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<tr>
<td></td>
<td><strong>Tricyclic antidepressants</strong></td>
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<td></td>
<td><strong>Monoamine oxidase inhibitors</strong></td>
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<td>Arterial blood gases</td>
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<td>Lithium level</td>
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<td>imaging scan of the head</td>
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NMS: Management Principles

- Early recognition
- Exclusion of alternative diagnosis
- Withdrawal of offending drug(s)
- Supportive care
- Specific Treatments
Supportive Care

- Hydration
- Electrolyte balance
- Control hyperthermia
- Renal function
- Cardio-respiratory Support
- Managing agitation
Specific Drug Treatments

- Agitation: diazepam
- Dopaminergic drugs:
  - bromocriptine (postsynaptic) 2.5-15mg tds
  - amantadine (presynaptic) 100-200mg bd
  - Levodopa/ cabergoline
- Muscle Relaxants:
  - diazepam
  - dantrolene (IV or oral) 1-10mg/kg/d
- ? Methylprednisolone pulse ivi (Sato et al 2005)
- ? ivi Na valproate
- DO NOT GIVE: anticholinergics
Hierarchy of Interventions

- **Mild NMS**
  - supportive, benzodiazepine

- **Moderate NMS**
  - supportive, benzodiazepine, bromocriptine/amantadine, oral dantrolene, ECT

- **Severe NMS**
  - ICU, supportive, IVI dantrolene, diuresis, plasma exchange, ECT
Monitoring in Established NMS

- Daily review by medical staff
- Observations: temp, BP, Pulse tds
- CK, UEC, LFT, FBC.
- Monitoring for complications: infections, pressure areas, dehydration.
- Note any changes in mental state or rigidity
Approach to Suspected NMS

- Monitor as if patient has NMS.
- Cease neuroleptic in most situations.
- Look for signs: worsening confusion, rigidity, autonomic signs including incontinence.
- Observations: temp, BP, Pulse tds
- CK, UEC, LFT, FBC.
NMS: outcome

- Mortality: 4-25%
- Neurological:
  - persistent motor/cerebellar signs
  - persistent cognitive deficits
- General: contractures, complications
- Renal failure
NMS: Neuroleptic Rechallenge

- Recurrence rate variable (10-83%)
- Adequate Gap?
- Low potency or atypical neuroleptic
- Start low, go slow, no IMI
- Attend to risks (agitation, hydration)
- Clinical & biochemical monitoring
- ?ECT
ECT is relatively safe and effective treatment for NMS

Early-onset action (within the first six ECTs)

Polarising muscle relaxants e.g. suxamethonium appear safe