Putative novel pharmacological treatments for tic disorders: insights from animal models

Presented By:
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Disclosures

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Treatment algorithm of tic disorders

1. **Tic disorder**
   - Psychoeducation

2. **Presence of tics, but no indication for treatment**
   - **Yes**: Monitoring
   - **No**: **Presence of tics, but comorbid disorder(s) have treatment priority**

3. **Presence of tics, but comorbid disorder(s) have treatment priority**
   - **Yes**: Treatment of comorbid disorder(s)
   - **No**: **Indication for treatment of tics, with preference for (and availability of) behavioural treatment**

4. **Indication for treatment of tics, with preference for (and availability of) behavioural treatment**
   - **Yes**: Behavioural therapy (PRT, CBIT and ERP)
   - **No**: **Tics still with indication for treatment**

5. **Tics still with indication for treatment**
   - **Yes**: Combination of pharmacotherapy and behavioural therapy
   - **Yes** (combined): Combined pharmacotherapy with different agents
   - **Yes** (alternative): Alternative therapies in specialized centres (DBS, cannabinoids and botulinum toxin, among others)
   - **Yes** (pharmacotherapy): Pharmacotherapy

6. **Indication for treatment of tics, with preference for pharmacological treatment**

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## Pharmacotherapy of tic disorders

<table>
<thead>
<tr>
<th>Medications</th>
<th>Recommendation</th>
<th>Evidence quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>Weak</td>
<td>High</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Weak</td>
<td>High</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Weak</td>
<td>High</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Weak</td>
<td>Moderate</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>Weak</td>
<td>Very low</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Weak</td>
<td>Low</td>
</tr>
</tbody>
</table>

The development of new drug treatments for tic disorders with high efficacy, tolerability, and safety is an urgent and unmet need.

To date, most therapeutic developments for tic disorders have been based on the repurposing of already-approved drugs.
**Face validity**: analogy between the behavioral performance of the animal models and the signs/symptoms in TS

**Construct validity**: congruence between the pathophysiology of TS and the neurobiology of behaviors in animal models

**Predictive validity**: sensitivity of animal model to validated treatments (antipsychotics, clonidine etc.) or risk factors (stress, sleep deprivation, etc.)
Testing paradigms for face validity

Tic-like responses

- Tic-like manifestations in animals can vary from **rapid bursts** to **repetitive stereotypies**
- Differences may be related to the specific mechanisms driving the semivoluntary mechanism (i.e., focal inhibition in the striatum vs dopamine hyperactivity etc.)

Prepulse inhibition (PPI) of the startle

- PPI is the best-validated cross-species operational index for **sensorimotor gating**;
  - TS individuals exhibit PPI deficits
Pathophysiology of Tourette Syndrome

TS patients exhibit stronger neural activity in sensorimotor cortex, putamen, pallidum, and substantia nigra.

Activity in these areas correlate positively with tic severity.
Simplified schematization of CSTC circuitry

- CIN
- PVIN
- Striatum
- SNC
- MSN
- GPI
- RC
- Thalamus
- PFC
- SMC

Neurotransmitters:
- Glutamate
- GABA
- Acetylcholine
- Dopamine
Tics are related to areas of **hyperactivity in the striatum** (aberrant disinhibition foci), which override “center-on surround-off” contrast for the proper activation of desired motor pattern and silencing of competing movements.
Hyperactivation of medium spiny neurons leads to tics
Tics are the result of signal imbalances in medium spiny neurons.

**Excitatory signals:**
- Glutamate from cortex
- Glutamate from thalamus
- Dopamine from substantia nigra

**Inhibitory signals:**
- Acetylcholine from str. interneurons
- GABA from str. interneurons
- Prefrontal control on interneurons
Activation of sensorimotor cortex

Glutamate ➔ CIN ➔ Striatum ➔ PFC
GABA ➔ PVIN ➔ Striatum ➔ SMC
Acetylcholine ➔ SNC ➔ GPI
Dopamine ➔ SNC ➔ PVIN ➔ GPI

RC ➔ TICS

Thalamus ➔ TICS

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Activation of dopaminergic pathways

Glutamate
GABA
Acetylcholine
Dopamine

Striatum
CIN
MSN
PVIN
SNC
GPI
SMC
PFC
RC
Thalamus
TICS

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Striatal interneuronal deficits in TS

The striatum in TS features significant deficits in cholinergic (CIN), parvalbumin-GABAergic (PVIN) and Nitric Oxide Synthase1/Neuropeptide Y/Somatostatin-GABAergic interneurons (Kalanithi et al., 2005; Kataoka et al., 2011; Lennington et al., 2016)
Loss of interneurons

Glutamate
GABA
Acetylcholine
Dopamine

Striatum
PFC
SMC
RC

TICS
Thalamus

CIN
MSN
PVIN
SNC
GPI
Recent evidence shows that tic suppression increases PFC activity in TS

Some types of stress may reduce the ability to suppress tics → inhibitory effect on PFC
Developing animal models of TS

Identification of phenotypes in patients

Identification/replication of intermediate phenotypes in animal models

Development and validation of drugs and diagnostic biomarkers

**TRANSLATIONAL STRATEGY**
How do we generate animal models of TS?

Genetic manipulations:
Based on alterations of the key genes associated with TS.

Environmental manipulations:
Based on exposure to factors associated with higher risk for TS.

Pharmacological/lesional manipulations:
Based on reproducing the key neurotransmission and neurobiological abnormalities in TS.
## Animal models of Tourette syndrome

<table>
<thead>
<tr>
<th>GENETIC MANIPULATION</th>
<th>DAT1</th>
<th>PPI deficits, perseverative behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAOA</td>
<td>Perseverative and stereotyped behaviors</td>
</tr>
<tr>
<td></td>
<td>SLITRK1</td>
<td>Anxiety-like behaviors</td>
</tr>
<tr>
<td></td>
<td>NLGN4</td>
<td>Repetitive behaviors</td>
</tr>
<tr>
<td></td>
<td>CNTNAP2</td>
<td>Perseverative and stereotyped behaviors</td>
</tr>
<tr>
<td></td>
<td>HDC</td>
<td>Perseverative and stereotyped behaviors</td>
</tr>
<tr>
<td></td>
<td>DLGAP3</td>
<td>Excessive grooming</td>
</tr>
<tr>
<td>ENVIRONMENTAL MANIPULATIONS</td>
<td>Early-life stress</td>
<td>Impulsivity, perseverative and stereotyped behaviors</td>
</tr>
<tr>
<td></td>
<td>Early-life inflammation</td>
<td>Increasing grooming and rearing</td>
</tr>
<tr>
<td>PHARMACOLOGICAL/LESIONAL MANIPULATIONS</td>
<td>Dopaminergic activation</td>
<td>PPI deficits, perseverative behaviors</td>
</tr>
<tr>
<td></td>
<td>Striatal GABAergic antagonism</td>
<td>Tics</td>
</tr>
<tr>
<td></td>
<td>Cortical neuropotentiation</td>
<td>Tics, Repetitive behaviors, PPI deficits</td>
</tr>
<tr>
<td></td>
<td>Interneuron depletion</td>
<td>Repetitive behaviors, PPI deficits</td>
</tr>
</tbody>
</table>
D1CT-7 mice: a model of cortical neuropotentiation
D1CT-7 mice are sensitive to hallmark TS therapies

Haloperidol (0.3 mg/kg, i.p.)

Clonidine (0.2 mg/kg, i.p.)

CIN-d mice: a model of striatal disinhibition

Cadeddu et al, Neuropsychopharmacology, 2023
CIN-d mice: a model of striatal disinhibition

Grooming stereotypies

Tic-like jerks

Cadeddu et al, Neuropsychopharmacology, 2023
CIN-d mice are sensitive to hallmark TS therapies

Cateddu et al, Neuropsychopharmacology, 2023
Can we use animal models to develop new treatments?

<table>
<thead>
<tr>
<th>New therapeutic targets</th>
<th>New putative treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosteroids - allopregnanolone</td>
<td>Isoallopregnanolone &amp; Finasteride</td>
</tr>
<tr>
<td>$M_4$ muscarinic receptors</td>
<td>Xanomeline, $M_4$ PAMs</td>
</tr>
<tr>
<td>5-HT$_{2A}$ serotonin receptors</td>
<td>Pimavanserin</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>?</td>
</tr>
<tr>
<td>GABA-A receptors ($\alpha6$)</td>
<td>DK-I-56-1</td>
</tr>
</tbody>
</table>
5α- reductase 1 and 2 are the enzymes catalyzing the rate-limiting step of neurosteroidogenesis.

Adapted from Paba, Frau, Devoto, Marrosu, Bortoloto, Curr Pharm Des. 2011
Stress increases allopregnanolone in the PFC of mice

Cadeddu et al, Neuropsychopharmacology, 2023

Mosher et al, Sci Rep, 2017
Allopregnanolone produces TS-like manifestations in mice

Before AP | After AP
---|---

Mosher et al, 2017

**Grooming duration (s)**

**Acoustic PPI (avg %)**

AP-systemic | AP-mPFC
---|---

AP dose (µg/mouse)
Allopregnanolone activates GABA-A receptors

AP inhibits PFC functions by **activating GABA-A receptors** → **lower ability to suppress tics**
Stress reduces tic control via allopregnanolone

Diagram showing the neural circuitry involving various brain regions and neurotransmitters, such as Glutamate, GABA, Acetylcholine, and Dopamine, with arrows indicating direction and stress leading to an increase in AP.
• Approved by FDA for treatment of benign prostatic hyperplasia and alopecia in humans

• By blocking 5α-reductase, finasteride reduces the synthesis of several neuroactive steroids

• Finasteride also dramatically reduces AP synthesis in the PFC
Finasteride reduces TS-related behaviors in mice

D1CT-7

CIN-d

**Cadeddu et al, Neuropsychopharmacology, 2023**

**Mosher et al, Sci Rep, 2017**
Finasteride reduces tics in treatment-refractory TS patients

Muroni, Paba, Marrosu, Bortolato, 2011, Mov Disord

Bortolato et al, 2007, Am J Psych
The AP antagonist isoallopregnanolone (isoAP) reduces tic-like behaviors

Cadeddu et al., 2020, J Neuroendocrinol

Cadeddu et al., 2023, Neuropsychopharmacology

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Isoallopregnanolone (sepranolone) reduces tic severity in TS

YGTSS total tic score change from baseline, pediatrics and adults (mITT)

From: Heidi Biernat and Nanette Debes

<table>
<thead>
<tr>
<th>mITT population</th>
<th>Sepranolone + SoC</th>
<th>SoC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Week 4</td>
<td>-8.07</td>
<td>-5.56</td>
</tr>
<tr>
<td>Week 8</td>
<td>-8.72</td>
<td>-5.81</td>
</tr>
<tr>
<td>Week 12</td>
<td>-8.57</td>
<td>-3.94</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PP population</th>
<th>N=10</th>
<th>N=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>-10.72</td>
<td>-2.95</td>
</tr>
<tr>
<td>Week 8</td>
<td>-11.82</td>
<td>-4.35</td>
</tr>
<tr>
<td>Week 12</td>
<td>-9.92</td>
<td>-3.95</td>
</tr>
</tbody>
</table>

12 w
p=0.051 active vs SoC

Per-protocol (PP)
Patients having taken all doses as planned and all visits within predefined visit window

mITT
Patients having taken at least 6 doses per 4 weeks
IsoAP and finasteride suppress tics by restoring PFC function.
The M1/M4 agonist xanomeline reduces TS-related responses in mice.
The M1 antagonist VU0255036 does not counter the effects of xanomeline

**D1CT-7 model**

- Grooming duration (s)
- Jerks (n/min)
- Acoustic PPI (avg %)

**CIN-d model**

- Grooming duration (s)
- Jerks (n/min)
- Acoustic PPI (avg %)
The M1 agonist cevimeline does not reduce TS-related responses in mice.
The M4 receptor antagonist VU6028418 reverses the effects of xanomeline.

D1CT-7 model
- Grooming duration (s)
- Jerks (n/min)
- Acoustic PPI (avg %)

CIN-d model
- Grooming duration (s)
- Jerks (n/min)
- Acoustic PPI (avg %)
The M4 positive modulator VU0467154 reduces TS-related responses in mice.
M4 activation counters the effects of corticostriatal activation
M4 activation offsets the effects of low striatal acetylcholine.
The 5HT2A antagonist pimavanserin reduces TS-related responses in mice

Approved in 2016 for psychosis in Parkinson’s disease

5-HT$_{2A}$ receptors are overexpressed in the cortex of TS Patients (Haugbøl et al., 2007)

In a pilot study, pimavanserin reduced tics in TS patients (Billnitzer and Jankovic, 2021)
Pimavanserin also reduces aggression in D1CT-7 mice

Given the association of coprophenomena with aggression, we speculate that these data may signify that pimavanserin may be particularly appropriate for high-severity TS individuals with coprolalia and copropraxia.
THC reduces some TS-relevant phenotypes in a dose- and model-dependent fashion.

**D1CT-7 model**

- Grooming duration (s)
- Jerks (n / min)

**CIN-d model**

- Grooming duration (s)
- Acoustic PPI (avg %)

**Key Points**:
- THC reduces some TS-relevant phenotypes in a dose- and model-dependent fashion.
- Pimavanserin also reduces aggression in D1CT-7 mice.

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Animal models of TS are instrumental to study TS pathophysiology

Using complementary models of TS may be a key strategy to identify new therapeutic targets and putative treatments

Using different models of TS, we showed that stress may exacerbate symptoms via increased synthesis of the neurosteroid **allopregnanolone**

Therapies that reduce allopregnanolone synthesis (such as **finasteride**) or signaling (such as **isoallopregnanolone**) have a promising therapeutic effect in TS

Using the same strategy, we found that **M₄ activators** and **5-HT₂A antagonists** may be new putative therapeutic strategies for tic disorders
Acknowledgments

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