New and emerging agents in psychopharmacology

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Objectives

1. Describe new pharmacological strategies for the treatment of psychiatric conditions
2. List recently approved psychopharmacological agents, and discuss their potential uses within the context of standard therapy
3. Evaluate evidence for the use of investigational psychopharmacological agents

A brief history of psychopharmacology
History

1st Period – Late 19th century
- Followed the isolation of morphine from opium in 1806
- Major discoveries:
  - Morphine for pain and agitation
  - Potassium bromide for epilepsy and anxiety
  - Chloral hydrate for insomnia
- Trend towards behavioural management via pharmacology rather than physical restraint

2nd Period – Early 20th century
- Introduction of barbiturates for sedation, insomnia, seizures, and general anesthesia
- Major discoveries:
  - Barbital (1903), phenobarbital (1912)
  - Amphetamine for narcolepsy (1935)
  - Insulin coma for schizophrenia (1940s)

3rd Period – Mid 20th century, present
- Explosion of effective ‘psychotropic’ drugs:
  - Lithium (1949)
  - Chlorpromazine (1952), haloperidol (1959)
  - Reserpine (1954)
  - Meprobamate (1956)
  - Iproniazid (1957)
  - Imipramine (1957), amitriptyline (1961)
  - Chlordiazepoxide (1960)
History

Theories - Schizophrenia
- Dopamine hypothesis (1963):
  - Antipsychotic effect due to DA receptor blockade
- Typical antipsychotics:
  - Post-synaptic D_2 blockade in nigrostriatal pathways responsible for antipsychotic effect AND extrapyramidal symptoms (EPS)
- Atypical antipsychotics:
  - Weaker, transient ("fast-off") D_2 blockade
  - 5-HT_2A antagonism hypothesized to reduce EPS

Theories - Depression
- Monoamine hypothesis (1965):
  - Depression results from depletion of CNS serotonin (S-HT), norepinephrine (NE), and dopamine (DA)
  - Supported by:
    - Depressive effect of reserpine
    - Proposed antidepressant MOAs of antidepressants (i.e. increasing synaptic monoamine conc.)
  - Revised theory proposes a modulatory role for monoamine depletion

New theories in psychopharmacology
New Theories

**Glutaminergic dysfunction**
- May be involved in pathophysiology of depression
- Proposed mechanisms:
  - Hyper- / hypoactivity NMDA glutaminergic receptors
  - Changes in glutamate / glutamine concentrations
  - Modulatory effect of monoamine depletion
- Supporting evidence:
  - Ketamine produces rapid antidepressant effect in patients with Major Depressive Disorder (MDD)

**NMDA receptor**


New Theories

**Glutaminergic dysfunction**
- Ketamine:
  - Non-competitive NMDA receptor antagonist
  - Binds to ion channel binding site, blocking Ca²⁺ influx
  - A review of 12 RCT’s reported:
    - Ketamine 0.5 mg/kg IV produces rapid but transient antidepressant effect in MDD
    - May also be effective via intranasal route
New Theories

Glutaminergic dysfunction
- Controversy:
  - Other NMDA antagonists (e.g., memantine, lanicemine) that bind to similar sites within the NMDA ion channel have failed to produce similar antidepressant effects
  - Suggestive that other mechanisms are involved in the antidepressant effect of ketamine

New Theories

NMDA hypofunction hypothesis
- Proposes that NMDA receptor hypofunction explains the symptoms and course of schizophrenia
- Supportive evidence:
  - Phencyclidine (NMDA antagonist) induces a schizophrenia-like psychosis
  - Long-term induced NMDA hypofunction has been linked to structural changes in corticolimbic regions in animal models

New Theories

NMDA hypofunction hypothesis
- Lead to the investigation of direct and indirect NMDA co-agonists, including:
  - Glycine, D-serine
  - Sarcosine
- Clozapine was shown to interact with glycine co-agonist binding site on NMDA:
  - May help explain enhanced efficacy of clozapine in treatment-resistant schizophrenia
New Theories

The 'tripartite synapse'

- Astrocytes are the most abundant form of glial cell:
  - Support CNS neurotransmission
  - Not previously believed to play an active role in synaptic transmission
- New evidence demonstrates that astrocytes:
  - Express receptors for most neurotransmitters
  - Release neuroactive substances (gliotransmitters)
  - Dynamically regulate neurotransmitter turnover

New Theories

The 'tripartite synapse'

- 'Tripartite synapse' refers to a new model of the synapse that integrates:
  - Pre-synaptic neuron
  - Post-synaptic neuron
  - Surrounding astrocytes

New Theories

The 'tripartite synapse'

- Astrocytes may play important roles in the pathogenesis of mental disorders
- E.g., decreases in glial D-serine lead to NMDA receptor dysregulation associated with schizophrenia
- Reduced astrocyte cell number is associated with depression
New Theories

De-myelination

- Myelination:
  - Major constituent of white matter
  - Insulates neuronal axons to increase conduction speed
- Oligodendrocytes are glial cells that form myelin sheaths around neuronal axons
- Dysfunction of myelination and oligodendrocyte function linked to pathology of schizophrenia

- Some atypical antipsychotics have been shown to increase myelin volume by activating lipid biosynthetic genes
- Rates of hypertriglyceridemia correlates with clinical improvement with clozapine
- May be a contributing factor in clozapine’s efficacy in treatment-resistant schizophrenia

Question

Novel antipsychotic treatments have been proposed that target neuroinflammation:

a) True
b) False

Question

Ketamine produces a rapid antidepressant effect in patients Major Depressive Disorder:

a) True
b) False
Ketamine produces a rapid antidepressant effect in patients Major Depressive Disorder:
   a) True
   b) False

Recently approved psychopharmacological agents

Aristada

Overview
   • aripiprazole lauroxil (Aristada)
   • Atypical antipsychotic
   • Long-acting injectable
   • Approved October 2015 for treatment of:
     - Schizophrenia
Aristada

How supplied
- Single-use pre-filled syringe:
  - 441 mg / 1.6 mL
  - 662 mg / 2.4 mL
  - 882 mg / 3.2 mL
- AWP:
  - 441 mg ($1266.00)
  - 662 mg ($1899.60)
  - 882 mg ($2530.80)


Aristada

Dosing
- Patient must be accessed on oral aripiprazole prior to initiation of Aristada
- Dosing options:
  - 441 mg IM monthly (= 10 mg PO daily)
  - 662 mg IM monthly (= 15 mg PO daily)
  - 882 mg IM monthly (= 20mg PO daily)
  - 882 mg IM every 6 weeks
- Administer aripiprazole PO for first 21 days


Aristada

Dosing
- Concomitant use of strong CYP3A4 or 2D6 inhibitors:
  - Continue 441 mg if tolerated
  - Reduce 662 mg or 882 mg dose to next lower strength
- Concomitant use of strong CYP3A4/2D6 inhibitors:
  - Only 441 mg dose is recommended
- Concomitant use of CYP3A4 inducers:
  - Continue 662 mg or 882 mg dose
  - Increase 441 mg to 662 mg

Aristada

Precautions
- In elderly patients with dementia-related psychosis, increased risk of death (BBW) and CVA
- Neuroleptic Malignant Syndrome
- Metabolic changes
- Orthostatic hypotension
- Leukopenia, neutropenia, agranulocytosis
- Seizures
- Potential for cognitive and motor impairment

Clinical trials
- Multicenter, RCT (n=596)
- Patients aged 18 – 70 yrs with schizophrenia
- Compared Aristada 441 mg vs 882 mg vs placebo
- Primary outcome: Change in Positive and Negative Syndrome Scale (PANSS) score from baseline-day 85
- Both doses significantly improved PANSS by day 85
- Major TEAE: akathisia (11.5, 11.6%)

Conclusion
- Like other LAIs, Aristada may improve adherence-related treatment outcomes
- Optional dosing every 6 weeks
- Comparable pricing to other LAIs
Rexulti

Overview
- brexpiprazole (Rexulti)
- Atypical antipsychotic
- Once daily oral tablets
- Approved July 2015 for treatment of:
  - Schizophrenia
  - Major Depressive Disorder (adjunctive to antidepressants)


Rexulti

How supplied
- Oral tablets:
  - 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg
  - AWP (all strengths)
  - $1038.60 (30 tablets)


Rexulti

Pharmacology
- Similar profile to aripiprazole
- D₂ partial agonist
- 5-HT₁₅ partial agonist
- 5-HT₂₅ antagonist
- Alpha-1b and 2c antagonist

Rexulti

Pharmacokinetics
- $T_{\text{Max}}$ 4 hrs
- Absorption not affected by food
- Extensively distributed ($V_d \sim 1.6 \text{ L/kg}$)
- Highly protein bound (>99%)
- Metabolized primarily by CYP3A4 / 2D6
- No active metabolites
- Excretion: urine (25%), feces (46%)
- $t_{1/2}$ 86 – 91 hrs

Rexulti

Dosing
- Schizophrenia:
  - Initial dose: 1 mg / day
  - Recommended dose: 2 – 4 mg/day (DNE 4 mg)
- Major Depressive Disorder:
  - Initial dose: 0.5 – 1 mg / day
  - Recommended dose: 2 mg / day (DNE 3 mg)

Dosing
- Renal adjustment (CrCL < 60 mL/min):  
  - Schizophrenia: DNE 3 mg/day
  - Major Depressive Disorder: DNE 2 mg/ day
- Hepatic adjustment (Child-Pugh >/= 7):
  - Schizophrenia: DNE 3 mg/day
  - Major Depressive Disorder: DNE 2 mg/ day
**Rexulti**

**Dosing**
- Concomitant use of a strong CYP3A4 or 2D6 inhibitor:
  - Administer 50% of usual dose
- Concomitant use of both strong/moderate CYP3A4 and 2D6 inhibitors:
  - Administer 25% of usual dose
- Concomitant use of a CYP3A4 inducer:
  - Double usual dose (over 1 – 2 weeks)

**Precautions**
- In elderly patients with dementia-related psychosis, increased risk for death (BBW) and CVA
- Increased suicidality in patients <= 24 yo (BBW)
- Neuroleptic Malignant Syndrome
- Tardive Dyskinesia
- Hyperglycemia, dyslipidemia, weight gain

**Precautions**
- Leukopenia, neutropenia, agranulocytosis
- Orthostatic hypotension and syncope
- Seizure
**Rexulti**

**Clinical trials – Schizophrenia**
- Approval based on two 6-week RCTs (n=623, 657)
- Patients aged 18 – 65 yo with schizophrenia
- Compared brexipiprazole 1mg, 2 mg, 4 mg vs placebo
- Efficacy scales:
  - Positive and Negative Syndrome Scale (PANSS)
  - Clinical Global Impressions-Severity (CGI-S)
- Primary outcome: Change in PANSS from baseline-week 6

Schizophr Res. 2015;164:127-35.

2 mg and 4 mg doses significantly decreased PANSS total score by week 6 vs. placebo (-4.78, p=0.0093)
- No TEAEs occurring in >= 5% of treatment groups
- No significant difference in...

**Vraylar**

**Overview**
- cariprazine (Vraylar)
- Atypical antipsychotic
- Once daily oral capsules
- Approved September 2015 for treatment of:
  - Schizophrenia
  - Bipolar I (acute mania / mixed episodes)
Vraylar

How supplied

- Oral capsules:
  - 1.5 mg
  - 3 mg
  - 4.5 mg
  - 6 mg
- Pricing unavailable


Vraylar

Pharmacodynamics

- D₃ and D₂ receptor partial agonist:
  - 10-fold greater affinity for D₃ than D₂
  - May improve cognitive activity
- 5-HT₂₆ antagonist
- 5-HT₁A agonist
- Prolactin-sparing


Vraylar

Pharmacokinetics

- T_max 2 – 6 hours
- Absorption not affected by food
- 91 – 97% protein bound
- Metabolized extensively via CYP3A4
- Forms two equipotent active metabolites
- Excreted ~21% in urine (1.2% unchanged)
- T½ 2 – 4 days (1 – 3 weeks for active metabolite)

**Vraylar**

**Dosing**
- **Schizophrenia:**
  - Initial dose: 1.5 mg
  - Recommended dose: 1.5 – 6 mg
- **Bipolar mania:**
  - Initial dose: 1.5 mg
  - Recommended dose: 3 – 6 mg

**Precautions**
- In elderly patients with dementia-related psychosis, increased risks of death (BBW) and CVA
- Neuroleptic malignant syndrome
- Tardive dyskinesia
- Metabolic: hyperglycemia, dyslipidemia, weight gain
- Orthostatic hypertension

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**Vraylar**

**Dosing**
- Concomitant use of a strong CYP3A4 inhibitor:
  - Reduce Vraylar dose by 50%
- Concomitant use of a CYP3A4 inducers:
  - Use of Vraylar is not recommended
- No renal or hepatic dose adjustments

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**Vraylar**

**Package Insert**
**Vraylar**

**Clinical trials – Schizophrenia**

- Approval based on three 6-week RCTs
- Patients aged 18 – 60 yrs with schizophrenia
- Outcomes:
  - Change in PANSS from baseline-week 6 (Primary)
  - Change in CGI-S from baseline-week 6 (Secondary)

*Schizophr Res.* 2014;152:450-7.
*Eur Neuropsychopharmacol.* 2013;23(suppl 2):5477-5478.

Cariprazine demonstrated superior efficacy to placebo in all three trials

- Cariprazine was not directly compared to active controls: risperidone (4 mg), aripiprazole (10 mg)
- Studies suggest lower incidence of weight gain, metabolic changes, and hyperprolactinemia

*Schizophr Res.* 2014;152:450-7.
*Eur Neuropsychopharmacol.* 2013;23(suppl 2):5477-5478.
Vraylar

Clinical trials – Bipolar mania
- Approval based on three 3-week RCTs
- Patients aged 18 – 65 yrs with bipolar 1 disorder
- Efficacy scales:
  - Young Mania Rating Scale (YMRS)
  - Clinical Global Impressions-Severity Scale (CGI-S)
- Outcomes: decrease in YMRS (primary) and CGI-S (secondary) from baseline at 3-weeks
- Superior efficacy over placebo in all three studies

Vraylar

Conclusions
- Current evidence is suggestive of adequate efficacy and potentially favorable tolerability
- Short follow-up (no evidence of long-term efficacy / safety)
- Lack of direct comparative efficacy data against active controls
- Potential pharmacoeconomic burden

Question
Vraylar (cariprazine) was approved in September of 2015 for the treatment of Treatment Resistant Depression:
a) True
b) False
Question
Vraylar (cariprazine) was approved in September of 2015 for the treatment of Treatment Resistant Depression:
   a) True
   b) False

Investigational agents

Investigational
Triple reuptake inhibitors
• Investigational drug class:
  - Inhibit reuptake of NE, 5-HT, and DA
• Some agents chemically related to venlafaxine, milnacipran, and bicifadine
• Sibutramine was formerly marketed as an anorexiant
• Tesofensine is currently being investigated for weight loss
**Investigational**

**Agometatine**
- Melatonergic antidepressant
- Exhibits MT1, MT2 agonism with 5-HT\textsubscript{2C} antagonism
- Failed to achieve FDA approval for depression
- Investigational indications include:
  - Bipolar depression
  - Seasonal Affective Disorder (SAD)
  - Generalized Anxiety Disorder (GAD)
  - Alcohol-dependent associated sleep disturbances

**Investigational**

**NMDA receptor modulators**
- Rapastinel (GLYX-13)
  - Partial agonist of NMDA glycine co-agonist binding site
  - Under investigation for adjunctive therapy of treatment-resistant depression

**Investigational**

**NMDA receptor modulators**
- Esketamine:
  - Potent non-competitive NMDA antagonist
  - S(+) enantiomer of ketamine
  - Under investigation for treatment of treatment-resistant depression
  - Developed by Johnson & Johnson as a nasal spray
Thank you!

References


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