Novel Antidepressants in Development: How They Differ from Current Medications

Norman Sussman, MD
Professor of Psychiatry
Director, Treatment Resistant Depression Program
Medical Director, The Steven and Alexandra Cohen Military Family Clinic
New York University School of Medicine
Where are we now?

- 60 years after the introduction of the MAOIs and TCAs all FDA approved antidepressants are still monoamine-mediated
- Up to two-thirds of treated patients fail to achieve full remission with existing drugs
- Tolerability and safety remain obstacles to compliance
We need antidepressant treatments that are....

- Rapid
- Robust
- Durable
- Safe
- Well tolerated
Two Basic Drug Development Strategies

• Expand number of monoamine neurotransmitter systems/receptors targeted by a new drug
• More selectively target norepinephrine and dopamine system
• Target alternative, non-monoamine CNS receptors

Of interest: Current drugs in development are being positioned as a second-line or augmentation treatment after first-line antidepressants have failed
Promising late-stage pipeline products into the market

- GLX-13 and NRX-1074
  - NMDA receptor: Glutamate and Glycine
- ALKS-4561
  - Opioid system
- Tedatixetine (Lu AA24530)
  - Reported to act as a triple reuptake inhibitor (5-HT > NE > DA) and in addition as a 5-HT2A, 5-HT2C, 5-HT3 and α1A-adrenergic receptor antagonist
- Edivoxetine (LY2216684)
  - Norepinephrine reuptake inhibitor (NERI)
NMDA (N-methyl-D-aspartate) Receptor Modulators: GLX-13 (Rapastinel) and NRX-1034

The concept of targeting NMDA receptors stems from clinical observations and studies showing that ketamine can rapidly improve depression symptoms (albeit with many risks)
There are two separate subunit families that go to make up the NMDA receptor, the GluN1 and GluN2 subunits. Glycine binds to the GluN1 subunit while glutamate binds to the GluN2 subunit.

NMDA receptor ligands can demonstrate rapid antidepressant effects (ketamine)
GLX-13 (Rapastinel) and NRX-1034

- The mechanism of action and effects are similar for both drugs: Partial agonism of the glycine site of the NMDA receptor
- Both molecules are well-tolerated and lack the schizophrenia-like psychotomimetic effects of other NMDA receptor antagonists such as ketamine
- Rapastinel (GLX-13) and NRX-1034 both have shown rapid antidepressant effects in preclinical models of depression.
- Rapastinel (GLX-13) is not orally-active (only being developed to be given IV)
NRX-1074 for MDD

• It is the only orally active NMDA receptor modulator with robust clinical trial results

• In a phase II single-dose study a single IV dose resulted in a statistically significant improvement in depression scores within 24 hours

• As of 2014, NRX-1074 was still in a phase II clinical trial, but ready to go into phase III studies.
NRX-1074

• The average reduction in HDRS-17 scores at 24 hours (at optimal dose) was 14 points, with a mean difference from placebo of 7 points (p=0.0029).

• The effect size observed at 24 hours was 0.88 – more than double the effect size seen with most other antidepressant drugs after 4 to 6 weeks of repeated dosing.

• Clinical response significantly different from placebo—72% of subjects on the highest dose of the compound demonstrated a clinically meaningful response at 24 hours (at least a 50 percent reduction in HDRS-17 score from baseline) compared to 39 percent of subjects given placebo (p=0.038).

• Clear dose response observed across all doses
Rapastinel (GLX-13)
(Repastinel) GLYX-13 Phase 2b Study

- Over 500 subjects to date
- Repeat-dose adjunctive treatment resulted in robust and sustained antidepressant effects in subjects with inadequate responses to their current antidepressants.
- No drug-related serious adverse events reported, including no sign of the psychotomimetic, or psychosis-like, effects associated with ketamine (an earlier Phase 2 single-dose study of GLYX-13 also documented rapid onset of antidepressant activity in as little as two hours).
- Repeated treatments produced a sustained response.
GLX Phase 2a

- A significant reduction in depressive symptoms was seen in as little as two hours following a single injection of GLYX-13 in subjects who had failed treatment with one or more antidepressant agents.
- The effect persisted for an average of seven days.
- The effect size observed at 24 hours and at seven days after a single administration of GLYX-13, was nearly double the effect size seen with most other antidepressant drugs after four to six weeks of repeated dosing.
GLYX-13 Phase 2b Study Design

• N = 386
• Divided into three parts:
  – a six-week adaptive-dose treatment stabilization period,
  – followed by a six-week randomized withdrawal period
  – then a four-week wash-out period.
• All given an IV bolus at start of the treatment stabilization period.
• All received weekly injections of drug until a response was established (reduction in HDRS-17 to less than or equal to 50 percent of pre-dose baseline).
• Upon achieving response, subjects were then dosed with weekly intravenous injections of placebo to force a relapse in depressive symptoms (increase in HDRS-17 to a score greater than 50 percent of pre-dose baseline).
• Upon relapse, subjects were again dosed with GLYX-13 to evaluate whether efficacy could be reestablished.
• This cycle was repeated with weekly doses of either GLYX-13 or placebo for six weeks.
• On average, subjects received four injections of GLYX-13 and two injections of placebo during this period.
GLYX-13 Phase 2b Study Design

- On average, subjects received four injections of GLYX-13 and two injections of placebo during this period.
- Those who didn’t respond during the stabilization period were excluded prior to the randomized withdrawal period.
- During this six-week withdrawal period, subjects were randomized to continue receiving GLYX-13 or to have the drug withdrawn and replaced with placebo. During the following four-week washout period, all subjects received injections of placebo.
GLYX-13 Phase 2b Study Design

- Subjects who did not respond during the stabilization period were excluded prior to the randomized withdrawal period.
- During this six-week withdrawal period, subjects were randomized to continue receiving GLYX-13 or to have the drug withdrawn and replaced with placebo.
- During the following four-week washout period, all subjects received injections of placebo.
In Phase 2b study GLYX-13 demonstrated an ability to induce and reestablish antidepressant effect

- It was able to again alleviate symptoms after a forced relapse, and its efficacy in reducing symptoms of depression increased over the course of the treatment period.

- Responders demonstrated a significant difference between responses to drug versus placebo during the treatment stabilization period, showing an average 2.8 point decrease in HDRS-17 scores in the week after receiving GLYX-13 and an average 3.1 point increase in HDRS-17 scores (worsening of depressive symptoms) in the week after receiving placebo (p-value = 0.03).

- During the treatment stabilization period, reductions in depression scores were compounded incrementally with each dose. For subjects responding, the first dose of GLYX-13 resulted in an average reduction in HDRS-17 scores of 4.9 points from baseline; this effect increased to a cumulative average reduction in HDRS-17 scores of 12.5 points from baseline by the end of the six-week stabilization period.

- No drug-related serious adverse events and no subjects discontinuing treatment due to drug-related adverse events.
CERC-301

- Orally-active, selective NMDA receptor subunit 2B (NR2B, NMDA receptor subunit 2B NR2B (also known as GluN2B) antagonist under development as an adjunctive therapy for TRD.
- In November 2013, phase II clinical trials were initiated, and in the same month, CERC-301 received Fast Track Designation from the FDA for TRD.
- A pilot study was published in 2012, and a phase 2 trial was completed in 2014.
CERC-301

• NMDA modulator
• Demonstrated preliminary signs of efficacy in a small exploratory study in TRD by the NIMH in which subjects reported a rapid onset of antidepressant effect, as early as five days after treatment.
• This study did not find clinically significant elevations in blood pressure, dissociative adverse effects, or serious adverse effects.
• In addition, the biomarker brain-derived neurotrophic factor (BDNF), improved significantly after nine days of treatment.
Opioids as Antidepressants

- Morphine
- Codeine
- Hydrocodone
- Oxycodone
- Methadone
- Fentanyl
- Diamorphine (heroin)

- Buprenorphine
- Tramadol

Not all opioids are the same!
Marked interindividual differences in clinical response!
ALKS-5461: An Opioid Modulator

A combination drug formulation:

buprenorphine + samidorphan (ALKS 33)

Under development as an adjunct to antidepressant therapy in TRD
Buprenorphine Pharmacology

- Partial agonist with high affinity for μ receptor
- Antagonist at Kappa receptor
- Relevant Pharmacokinetic Considerations:
  - Requires conversion to become analgesic (\(N\)-dealkylation catalyzed by CYP3A4): may explain why some patients don’t benefit from buprenorphine
  - Genetics, grapefruit juice and many medications (including fluoxetine and fluvoxamine) can reduce a person’s ability to metabolize buprenorphine into its bioactive form
Mu and Kappa Opiate Receptors
Functionally opposing endogenous opioid systems that regulate emotional and perceptual experience

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Agonist Effects</th>
<th>Antagonist Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu (µ)</td>
<td>• analgesia</td>
<td>• anxiety</td>
</tr>
<tr>
<td></td>
<td>• euphoria</td>
<td>• hostility</td>
</tr>
<tr>
<td>MOPr *</td>
<td>• antidepressant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• anxiety</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• dysphoria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• depression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• stress-induced anxiety</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• analgesia</td>
<td></td>
</tr>
<tr>
<td>KOPr</td>
<td>• dysphoria</td>
<td>• antidepressant</td>
</tr>
<tr>
<td>Kappa (K)</td>
<td>• depression</td>
<td></td>
</tr>
</tbody>
</table>

* Principal therapeutic opiates are selective for MOPr

Chavkin C. Neuropsychopharmacology (2012) 38, S1–S78
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Agonist Effects</th>
<th>Antagonist Effects</th>
</tr>
</thead>
</table>
| Mu (μ) MOPr * | • analgesia  
              • euphoria  
              • anxiety | ALKS-33               |
| Kappa (K) KOPr | • analgesia  
              • dysphoria  
              • depression  
              • stress-induced anxiety | Buprenorphine |
Buprenorphine Treatment of Refractory Depression

Comparison of clinical measures pretreatment, at 1 week, and at the conclusion of the buprenorphine trial in seven subjects completing 4 to 6 weeks of treatment

3 subjects were unable to tolerate more than two doses because of side effects. The remaining seven completed 4 to 6 weeks of treatment. As a group, they showed clinically striking improvement in both subjective and objective measures of depression. Much of improvement observed by end of 1 week of treatment and persisted throughout the trial. 4 subjects achieved complete remission of symptoms by the end of the trial (HDRS less or equal to 6), 2 were moderately improved, and one deteriorated.

Intranasal Buprenorphine as an Antidepressant: Patient 1

- Rapid buprenorphine titration to 0.15 mg TID.
- Progressive improvement in depression and anxiety over three weeks, with dose upped to 0.6 mg/day, which was the dosage for the remainder of the 6-week study, by which time, he was virtually asymptomatic.
- By that time, he had returned to his research and writing. Over the next few months, his dosage was raised to 0.3 mg TID and 0.45 mg at HS.
- Felt he had not only recovered from depression, but had achieved a new level of well-being and hopefulness. He reported much more subtle subjective effects of buprenorphine compared with his prior experience with opiates and particularly noted both a lack of acute euphoria and an absence of tolerance to the mood-elevating effects over time.
- He has remained on his present dose for over 2 years.

ALKS 5461: Opioid Receptor Modulator

- Consists of buprenorphine, a partial agonist, and ALKS 33, a potent mu-opioid antagonist,
- Designed to be a once-daily, non-addictive medicine.
- Early clinical development of ALKS 5461 was funded through a grant from the National Institute on Drug Abuse (NIDA).
ALKS 5461

• Following very positive (well-tolerated and significantly improved depression scores on 7 days) phase II trial results (multi-center, placebo-controlled, multi-dose study in 32 patients) ALKS-5461 was granted Fast Track Designation by the FDA for TRD in October 2013

• During 2014, three major phase III clinical trials were initiated in the US to evaluate core efficacy for the use of ALKS-5461 as an adjunctive treatment for patients who have had an inadequate treatment response to antidepressant monotherapy
Results from ALKS 5461 FORWARD-1

• A randomized, double-blind, parallel-arm study designed to evaluate the safety and tolerability of two titration schedules of ALKS 5461. In addition, the study assessed the efficacy of ALKS 5461 over an eight-week period, compared to baseline, in patients with MDD.

• Significantly reduced depressive symptoms from baseline starting at week one and continued to the end of the treatment period at week eight.

• The observed changes from baseline were clinically meaningful and statistically significant (p<0.001).

• There were no serious adverse events reported in the study (most common adverse events were nausea, constipation and dry mouth).
ALKS 5461: Expected Availability

• In January 2015, positive results from the first completed phase III study were presented.
• Results of additional pivotal phase III trials are expected in 2016.
• In addition, nine smaller supplementary studies will also be conducted, and will together conclude phase III research.
• Could be available next year
Edivoxetine (LY2216684)

- Norepinephrine reuptake inhibitor (NERI)
- The Phase III trials focused on meeting unmet needs of patients with MDD who had achieved only a partial response to treatment with an SSRI. Patients remained on SSRI treatment and received either edivoxetine or placebo
- Failed to meet primary endpoint of superior efficacy after 8 weeks of treatment in three Phase III trials.
- When added to an SSRI, did not separate from placebo in three acute randomized Phase III studies.
- Lilly will continue an ongoing clinical study evaluating the long-term maintenance effect of edivoxetine.
Tedatixetine (Lu AA24530)

- Early data showed significant improvements in depression scores over placebo with low drop out rates.
- Reported to act as a triple reuptake inhibitor (5-HT > NE > DA)
- In addition acts as a 5-HT2A, 5-HT2C, 5-HT3 and α1A-adrenergic receptor antagonist.
- It remains in phase II clinical trials.
- Considered phase III ready, but no phase III development reported yet
Amitifadine (EB-1010)

• Amitifadine (formerly EB-1010)
• A triple reuptake inhibitor: the greatest potency towards 5-HT reuptake, half as much towards NE reuptake and one eighth towards DA reuptake.
• This 1 to 2 to 8 ratio approximates the pharmacology of the two-product combination of citalopram and bupropion
Amitifadine (DOV-21,947 or EB-1010)

• Results in a small clinical trial indicated that amitifadine had statistically significant antidepressant effects and was well tolerated.
• In a phase IIb/IIIa, amitifadine did not meet its primary end point of a significant difference in MADRS score, compared with placebo.
• However, the lack of side effects seen with the 100 mg dose and signs of efficacy in post-hoc analyses suggest that MDD patients may benefit from higher doses.
Thank You