Why do new drugs cost so much?
An exploration of how Zulresso, the $34,000 treatment for post-partum depression, came to be and how the FDA requirement for demonstration of efficacy is inflating the cost of new drugs

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Abstract

• Why do new drugs cost so much? Is it because of clinical value and novelty, or because of commercial viability?

• This question can be answered through a case study of Zulresso, the first FDA-approved treatment for post-partum depression. It costs $34,000 dollars and doesn’t really work. Drugs just like it have been used for 60+ years. Xanax and progesterone, work the same way and probably would work equally well. So, Zulresso is not novel or clinically valuable.

• However, the manufacturer, Sage Therapeutics, has a $900 million dollar budget deficit, has only received $1.5 million in revenue so far from Zulresso (its only drug), and spent $100 million on research and development at the same time. This is typical operation for pharmaceutical companies. The current FDA requirement to prove efficacy for every disease indication by phase 3 clinical trials has inflated all costs – but has not guaranteed efficacy (Zulresso doesn’t really work).

• Given that FDA approval requiring demonstration of efficacy is not resulting in clinically valuable drugs for each the market, it may no longer be a useful feature. Instead, the FDA can take a strong stance on data transparency and marketing.
Introduction and Literature Review
When about 1 in 9 moms suffers from postpartum depression (PPD),

Each Day Matters.

ZULRESSO (brexanolone) is the first and only FDA-approved medicine specifically for postpartum depression in adults.
FDA approved Zulresso for treatment of post-partum depression on March 19, 2019

Composition:

- **Brexanolone** (the manufacturing name for allopregnanolone)
  - A neurosteroid produced in the brain as a metabolite of progesterone
- **Captisol** (a patent-protected excipient from the sulfobutylether-beta-cyclodextrin family)
  - Necessary to dissolve the extremely hydrophobic allopregnanolone in water

From pubchem.ncbi.nlm.nih.gov
How does Zulresso work?

Hormonal-withdrawal theory of post-partum depression (PPD)

- During pregnancy, most sex steroids have huge serum increases in free solubility, originating from the placenta
- The brain converts these into ‘neurosteroids’ which act as neurotransmitter modulators
- This causes altered receptor up/downregulation
- In the weeks after delivery, most sex steroids return to normal levels at a much faster rate than the receptor regulation
- Loss of receptor activity → depression

Known neuronal steroid metabolism pathways

Enzyme key
P450* = cytochrome proteins
StAR = Steroidogenic acute regulatory protein
n-HSD = hydroxysteroid dehydrogenase
(n=carbon atom bearing the hydroxyl)

Serum levels of sex steroids


Post-partum allopregnanolone/progesterone ratios in women with post-partum “blues”

Figure 1. Linear correlation between serum allopregnanolone and progesterone levels in euthymic women (A) and in women with postpartum “blues” (B).

Nappi RE et al. Serum allopregnanolone in women with postpartum “blues”. Obstetrics & Gynecology 2001 97(1):77-780
Women with a history of post-partum depression are more sensitive to hormonal withdrawal.

**FIGURE 1.** Mean Scores on the Cornell Dysthymia Scale Before and After Estrogen and Progesterone Replacement in Eight Women With a History of Postpartum Depression and Eight Normal Comparison Women*.

**FIGURE 2.** Mean Scores on the Cornell Dysthymia Scale at Baseline, After Addback and Withdrawal of Estrogen and Progesterone Replacement, and During Follow-Up for a Representative Woman With a History of Postpartum Depression*.

*Study phases: 8-week baseline, when no medications were administered; 4-week early withdrawal, when estradiol and progesterone, previously administered during an 8-week addback period, were withdrawn; and 8-week follow-up, when no medications were administered.

*Significant difference between baseline and withdrawal periods in the group with a history of postpartum depression (Bonferroni post hoc t test, p<0.01).

The fundamental theory underlying Zulresso is that replacing the sudden loss of allopregnanolone after delivery will treat post-partum depression.
CEO of Sage Therapeutics, Dr. Jeff Jonas, interview with CNBC – on what makes Zulresso so unique (and by implication, worth the price)

Salient points from interview:

- Zulresso uses a brand-new mechanism, never done by anyone ever before.
- Zulresso does not treat depression by altering neurotransmitter levels – instead, it ‘calms neural circuits’.
- Psychiatry is the only profession where alternative, non-medical therapies are accepted.
  - “If you walked into the doctor with diabetes, no one is going to argue if you should have nutritional counseling or insulin. You’re gonna get the medicine. But in depression people will say ‘maybe we don’t need medicine, maybe we should wait’”
- Zulresso is a game-changer because it tells women “its not your fault, you have a hormone imbalance, and we can correct it within two-three hours.”

Published 27 April 2019, "How a failed epilepsy drug became a $34,000 postpartum cure"
Unfortunately, none of these statements are a fully accurate depiction of Zulresso
Zulresso is not a novel drug – steroid derivatives have been used as anesthetics since the 1950s

- 1941 – Hans Seyle discovers intraperitoneal injection of steroid derivatives causes anesthesia in rodents
- 1954 case-control series demonstrates effective intravenous use of progesterone, dissolved in albumin/propylene glycol, for sedation and sleep induction
- 1957 Pfizer systematically tests structural derivations of steroids for maximal anesthetic effect – identifies allopregnanolone precursor as the most potent (but extremely water insoluble)
- 1957 hydroxydione succinate, a deoxycorticosterone derivative, is marketed as Viadril and Presuran – used extensively as an anesthetic
  - Extremely safe anesthesia, but slow onset/offset because low solubility required slow infusion
  - Well-documented superficial infusion pain and thrombophlebitis related to slow

<table>
<thead>
<tr>
<th>Steroid Derivative</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deoxycorticosterone acetate</td>
<td>Rapid anesthesia at low dose</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Rapid anesthesia at medium dose</td>
</tr>
<tr>
<td>Androsterone</td>
<td>Delayed anesthesia at high dose</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Delayed anesthesia at high dose</td>
</tr>
<tr>
<td>alpha-Estradiol</td>
<td>Light anesthesia at high dose</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>No effect</td>
</tr>
</tbody>
</table>

Zulresso is not a novel drug – steroid derivatives have been used as anesthetics since the 1950s

- 1973 – Glaxo Research markets alphaxolone, an allopregnanolone derivative dissolved in Cremaphor EL, for anesthesia in Europe and Australia (Althesin) and globally for veterinary medicine (Saffan).
  - It can be infused quickly and has no reports of thrombophlebitis – reputed to be the safest anesthetic on the market
- 1984 – Several high-profile case series of anaphylaxis in response to cremaphor EL results in removal of alphaxolone from human market (remains in use in cats to this day)
  - Notably most lipophilic drugs have been dissolved in this excipient, such as dizepam, cyclosporine, paclitaxol, doxorubicin, cisplatin – work is ongoing to find alternative excipients
- 1986/7 – Imperial Chemical Industries (now AstraZeneca) develops new anesthetic propofol which fills the same niche is dissolved in a soybean lipid oil emulsion and released worldwide, removing market incentive for a reformulation of Althesin
- 2017 – Drawbridge pharmaceuticals begins phase 3 clinical trials for a reformulation of alphaxalone in Captisol as an anesthetic

Zulresso initially was developed as an anti-convulsant agent for rescue therapy in status epilepticus (SE): this use is not novel (and it failed phase 3 trials for efficacy)

- 1960s - hydroxydione effect on EEG recordings noted to be anti-convulsant. Later work proved it was effective in preventing certain forms of drug-induced seizure

- Late 1970s – multiple case series showing the use of alphaxolone in SE, and ironically as an inferior anesthetic for electroconvulsive therapy since it shorted the length of induced seizures too much

- 1980s – mechanism of action determined for neurosteroids and alphaxolone (acts of GABA-A receptors) and compared to barbiturates and benzodiazepines

- 2001 – a comparison of the pharmacological and side-effect profiles of midazolam (a benzodiazepine) and allopregnanolone for anti-convulsant therapy found no clear clinical difference. To quote the author:

“Collectively, the results of this study, along with recently published data on the prolongation by i.c.v. [intracerebroventricular] injected allopregnanolone and midazolam of ethanol-induced sleep (Ż . Członkowska et al., 2000), indicate similar pharmacological and side-effects profiles of benzodiazepines and neurosteroids. Moreover, a similar efficacy of allopregnanolone and midazolam at the GABA receptors has been found. These findings, together with the conversion of neurosteroids in the brain to other steroid hormones (testosterone, estradiol, and aldosterone) (Baulieu, 1998), add to the accumulating evidence suggesting a less favorable pharmacological profile for this class of drugs than was previously thought.”

Zulresso initially was developed as an anti-convulsant agent for rescue therapy in status epilepticus (SE): this use is not novel (and it failed phase 3 trials for efficacy)

- 1997 – ganaxolone, another allopregnanolone derivative, is demonstrated to have efficacy in treating seizures in humans

- 2000 – ganaxolone is noted to be 3x more potent at treating catamenial epilepsy (menstruation-associated seizures) in a rodent model, linking its function explicitly to replacement of hormonal withdrawal

- 2003 – Marinus Pharmacueticals is founded to bring ganaxolone to market as an anticonvulsant

- 2011 Sage Therapeutics is founded to bring allopregnanolone (branded as Zulresso) to market as an anticonvulsant

Neurosteroids are not clearly differentiable from benzodiazepines and barbiturates as pharmacological agents

- 1986 – two influential papers, one in *Science*, show results generated in the laboratory of future Sage Therapeutics founder, Dr. Stephen Paul
- Precursors of neurosteroids do not inherently have electrophysiological activity – e.g. progesterone
  - The author notes the enzymes necessary to convert these to active neurosteroids are found in the brain
- Neurosteroids must have a hydroxyl or aldone group on carbon 3 and carbon 20, and reduction of the C4-C5 bond to be psychoactive
- Neurosteroids and alphaxolone all act on GABA-A receptors and increase the time the receptor is open (positive allosteric modulator (PAM))
  - This is by a different site than benzodiazepines, as they mutually enhance firing
- Neurosteroids have dose dependent effects; at low doses, they only have PAM activity – at high doses, they have direct receptor agonism
  - This property is precisely what is seen with the barbiturate pentobarbitol

Neurosteroids, barbiturates, and benzodiazepines have closely related pharmacodynamic profiles – likely interchangeable

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Year*</th>
<th>Company**</th>
<th>Mechanism of action</th>
<th>Clinical formulation - use</th>
<th>Known relevant side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>1912</td>
<td>Bayer</td>
<td>GABA-A receptor (alpha, beta, gamma/beta subunit interfaces): CAM (low) - holds chloride channel open longer Direct agonist (high) AMPA/kainate receptor: block Voltage-gated P/Q calcium channels (CaV2.1): inhibit</td>
<td>GABA agonism at low dose PAM at low dose Higher potency for CaV2.1 Enhances potassium inward-rectifiers (KIR) PAM activity on GABAR delta subunits (extrasynaptic GABA-R)</td>
<td>po, im, iv - epilepsy, convulsive SE, sedation po, im, iv, pr - ai/m, sedation, convulsive SE and the ‘medical coma’, anxiety, insomnia Same vein infusion pain, dramatic hypotension, myoclonic jerks rarely: propofol infusion syndrome (mitochondrial inhibition, usually ICU)</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>1930</td>
<td>Abbott Laboratories (AbbVie)</td>
<td>GABA-A receptor (alpha, beta, gamma/beta, ?delta-beta interface): PAM (low), direct agonist (high) Glycine receptor: PAM (low), direct action (high) Cholinergic receptors: inhibition voltage sodium channels: inhibition</td>
<td>iv, pr - ai/m, sedation</td>
<td>iv - ai/m, convulsive SE</td>
</tr>
<tr>
<td>Thiopental/ Methylxental</td>
<td>1935/ 1952</td>
<td>Abbott Laboratories</td>
<td>GABA-A receptor (alpha-gamma subunit interface): PAM - opens chloride channel more frequently Does not have affinity for GABA binding site.</td>
<td>po, iv - anxiety, convulsive SE, sedation, amnesia, muscular spasticity iv - convulsive SE, sedation, amnesia</td>
<td>additive, cognitive and memory impairment with both short- and long-term effects,</td>
</tr>
<tr>
<td>Propofol</td>
<td>1987</td>
<td>Imperial Chemical Industries (Astrazeneca)</td>
<td>GABA-A receptor (alpha-beta, gamma/beta, delta-beta interface): PAM (low), direct agonist (high)</td>
<td>Small vein infusion pain, thrombophlebitis</td>
<td>Anaphylactic reactions to the solvent, myoclonic jerks</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1962</td>
<td>Hoffman-La Roche</td>
<td>GABA-A receptor (alpha-gamma subunit interface):</td>
<td>iv - ai/m, convulsive SE</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>1982</td>
<td>Hoffman-La Roche</td>
<td>GABA-A receptor (alpha-gamma subunit interface):</td>
<td>iv - ai/m</td>
<td></td>
</tr>
<tr>
<td>Hydroxydione</td>
<td>1955</td>
<td>Pfizer</td>
<td>GABA-A receptor (beta-alpha subunit interface, delta subunit transmembrane section, ?delta subunit)</td>
<td>iv - ai/m</td>
<td>Small vein infusion pain, thrombophlebitis</td>
</tr>
<tr>
<td>Alphaxalone/ aldactolone (Althesin/Saffan)</td>
<td>1973</td>
<td>Glaxo Research (Glaxo-Smith-Kline)</td>
<td>GABA-A receptor (alpha-beta, gamma/beta, delta-beta subunit) PAM (low) - holds chloride channel open longer; target synaptic and extrasynaptic GABA-R</td>
<td>iv - ai/m</td>
<td>Anaphylactic reactions to the solvent, myoclonic jerks</td>
</tr>
<tr>
<td>Alphaxalone - SBE - BCD (Phaxan)</td>
<td>n/a</td>
<td>Drawbridge Pharmaceuticals</td>
<td>Direct agonist (high) Note - the general pharmacodynamic properties of each neurosteroid taken to clinical trials are very similar, but this is not representative</td>
<td>iv - ai/m (phase 1c trials completed)</td>
<td></td>
</tr>
<tr>
<td>Ganaxalone</td>
<td>n/a</td>
<td>Marinus Pharmaceuticals</td>
<td>GABA-A receptor (alpha-beta, gamma/beta, delta-beta subunit)</td>
<td>iv - convulsive SE (failed phase 3 trials)</td>
<td>Sedation, loss of consciousness,</td>
</tr>
<tr>
<td>Brexanolone - SBE - BCD (Zulresso)</td>
<td>2019</td>
<td>Sage Therapeutics</td>
<td>GABA-A receptor (alpha-beta, gamma/beta, delta-beta subunit)</td>
<td>iv - post-partum depression, convulsive SE (failed phase 3 trials)</td>
<td>Sedation, loss of consciousness, euphoria at high doses</td>
</tr>
</tbody>
</table>

- im intramuscular;
- iv intravenously;
- pr per rectum;
- po per ora (mouth);
- PAM - positive allosteric modulator;
- ai/m anesthesia induction/maintenance;
- SBEBCD (sulfobutylether beta-cyclodextran)
- *Year of clinical use.
- **original manufacturer (the company which now owns the original manufacturer)
- n.b. data in table is not exhaustive, but representative.
- Brand names and relevant excipients are included for the neurosteroids class

Progesterone therapy has also been tried for treatment of hormonal-withdrawal disorders (PMS, PPD, and menopause)

- 1953 – Dr. Katharina Dalton published on the symptomatology of premenstrual syndrome (PMS) and the effectiveness of IM progesterone to treat it – she publishes many cohort studies on this over the years
- 1959 - Publishes that synthetic progestins, because of certain chemical modifications, do not seem to be nearly as effective at treating PMS syndrome
- 1971 - publishes on the close similarities between PPD and PMS, hypothesizing a similar effect of hormonal withdrawal
- 1982 – human experimental study shows estrogen and progesterone improve mood in post-menopausal women
- 1985 – double blind crossover study shows progesterone is effective for PMS
- 1996 – transdermal estrogen demonstrated to be effective for treatment of severe postnatal depression
- 2000 – Pseudo-pregnancy model with leuprolide-induced hormonal withdrawal shows that progesterone replacement relieves symptomatology
- 2006 – Progesterone converts to allopregnanolone in both women with and without PMS and reduced symptoms
- 2014 – double blind placebo controlled study demonstrates progesterone reduces rate of post-partum cocaine use relapse
- 2016 – double blind placebo study demonstrates progesterone reduces rate of post-partum smoking relapse

Comparatively, Zulresso does not seem to have much promise for PPD. Women with severe PPD who received the 60hr infusion Zulresso show fewer depressive symptoms immediately after the: but remission rates are equivalent 30 days out.

Figure 3: Percentage change from baseline in mean HAM-D total score in the integrated BRX90 study population
p values were calculated by two-sided t test. BRX90=brexanolone injection 90 μg/kg. *p<0.05 vs placebo.

Figure S5: Patients with HAM-D remission in the integrated brexanolone injection 90 μg/kg/h study population
Remission was defined as achieving a HAM-D total score of ≤7. p-values were calculated by Z test from log transformation of the odds ratio. *Denotes statistical significance versus placebo, defined as p<0.05. PBO = placebo; BRX90 = brexanolone injection 90 μg/kg/hr.

Surprisingly high placebo response rate in Zulresso trial

- May relate to the 5 day hospitalization reducing caregiver burden. Selection from the methodological sections of the open-label phase 2 study and supplemental material:

“Vital signs were repeated every 12 hours throughout drug administration and the first day post-infusion. Clinical laboratory testing was repeated at 24, 48, and 84 hours after infusion initiation. Physical exam was repeated at 84 hours post infusion. Patients were contacted via telephone to monitor adverse events (AEs) (if they had been discharged from the PPIU) at Day 11 and Day 34. The Stanford Sleepiness Scale (SSS) was repeated at Hour 6 and at 12 hour intervals until Hour 60. Patients were discharged from the PPIU after Hour 84 assessments if clinically appropriate. Dosing was to be interrupted or discontinued in the event of a severe or life-threatening AE.”

“Participants received minimal compensation for participation in these studies, including travel expenses and day care costs for the in-clinic part of the study if required (i.e. no family member was available/able to care for children). Additionally, per each individual IRB’s requirements, a small stipend was paid on a per visit basis to compensate participants for their time.”

Non-pharmacological and SSRI therapy are more effective long-term than Zulresso

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Severity of PPD</th>
<th>N (treat/control)</th>
<th>Outcome</th>
<th>Treat</th>
<th>Control</th>
<th>Risk ratio (Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peer support therapy</td>
<td>Prevention</td>
<td>349/352</td>
<td>Percent who developed PPD after 12 weeks</td>
<td>14% *</td>
<td>25%</td>
<td>0.46 (0.24-0.62)</td>
</tr>
<tr>
<td>Intensive home visits by midwife/nurse</td>
<td>Prevention</td>
<td>881/782</td>
<td>Percent who developed PPD after 4 months</td>
<td>15% *</td>
<td>21%</td>
<td>0.68 (0.55-0.84)</td>
</tr>
<tr>
<td>Cognitive Behavioral Therapy</td>
<td>Mild</td>
<td>125/121</td>
<td>Percent who retained depression diagnosis after 1 year</td>
<td>51% *</td>
<td>74%</td>
<td>0.67 (0.46-0.97)</td>
</tr>
<tr>
<td>SSRI</td>
<td>Moderate</td>
<td>72/74</td>
<td>Percent who experienced remission by 6-8 weeks</td>
<td>49% *</td>
<td>26%</td>
<td>1.79 (1.08-2.98)</td>
</tr>
<tr>
<td>Zulresso (Integrated 90mcg/kg arm)</td>
<td>Moderate/Severe</td>
<td>102/107</td>
<td>Average % reduction of HAM-D scores 60hrs post-infusion</td>
<td>63% *</td>
<td>50%</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Percent who experienced remission 60hrs post-infusion</td>
<td>50% *</td>
<td>26%</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average % reduction of HAM-D scores 1 month post-infusion</td>
<td>62% *</td>
<td>56%</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Percent who experienced remission 1 month post-infusion</td>
<td>46%</td>
<td>44%</td>
<td>Not reported</td>
</tr>
<tr>
<td>ECT</td>
<td>Severe/psychosis</td>
<td>Only case series exist: generally high response rate (&gt;75%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The hypothesis behind this was reduced caregiving burden, just like the hospital visit would inherently entail.

Correspondence to the Lancet indicates other researchers question whether the Zulresso is merely a benzodiazepine mimetic/enhancer – Sage Therapeutics ignores its own CEO’s literature on benzodiazepines for depression

• One letter to the editor noticed that between 4-11% of the Zulresso group had received benzodiazepines, whereas 0-4% of the placebo group had. Sage Therapeutics response:
  
  "First, no published data support the use of benzodiazepines as effective antidepressants in humans. Second, most concomitant positive allosteric inhibitors used in our study were benzodiazepines, which do not share a common mechanism of action in post-partum depression as Tang and Parekh suggest."

• In actuality the CEO of Sage Therapeutics, Dr. Jeff Jonas, had previously published two papers on topics relevant to the use of alprazolam for depressive symptomatology during his time as chief medical officer at the company that sold it.

Abstract from 1993 paper: "We reviewed 84 active-drug-controlled studies with a total of 8,878 patients; 3,574 patients were treated with alprazolam, 3,666 were treated with another active drug, and 1,638 were treated with placebo. Two general findings emerged. First, alprazolam demonstrated efficacy for the treatment of anxiety disorders, panic disorder, and depression in the large majority of studies; for these illnesses, it appeared equal in efficacy to the active agents with which it was compared."

Abstract from 1996 paper: "The findings show no suggestion that use of alprazolam in depressed patients is associated with either the emergence or worsening of suicidal ideation. Neither the risk of emergence nor the risk of worsening of suicidal ideation was significantly different for alprazolam users than for placebo users. Rather, the majority of alprazolam users in these studies experienced improvement of suicidal ideation, and the rate of improvement of suicidal ideation was significantly greater for alprazolam users than for placebo users (71.9% vs. 57.7%)."


There is even high quality evidence showing alprazolam is effective therapy for PMS (which has similar etiology to PPD)

A Double-blind Trial of Oral Progesterone, Alprazolam, and Placebo in Treatment of Severe Premenstrual Syndrome

Ellen W. Freeman, PhD; Karl Rickels, MD; Steven J. Sondheimer, MD; Marcia Polansky, ScD

JAMA, July 5, 1995—Vol 274, No. 1

A double-blind trial of four medications to treat severe premenstrual syndrome

M.S.C. Diegoli*, A.M. da Fonseca, C.A. Diegoli, J.A. Pinotti
Department of Gynecology and Obstetrics, University of São Paulo, São Paulo, Brazil

Received 30 September 1997; received in revised form 27 January 1998; accepted 27 January 1998

Patients classification of patients according to the percentage of clinical evolution with each drug

<table>
<thead>
<tr>
<th>Groups</th>
<th>Worsening 6–24%</th>
<th>Recovery 0–24%</th>
<th>Recovery 25–49%</th>
<th>Recovery 50–74%</th>
<th>Recovery 75–100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>8 (26.7%)</td>
<td>11 (36.7%)</td>
<td>6 (20.0%)</td>
<td>5 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>7 (23.3%)</td>
<td>11 (36.7%)</td>
<td>7 (23.3%)</td>
<td>5 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>2 (6.7%)</td>
<td>9 (30.0%)</td>
<td>14 (46.7%)</td>
<td>5 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>7 (23.3%)</td>
<td>8 (26.7%)</td>
<td>9 (30.0%)</td>
<td>4 (13.3%)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1 (3.3%)</td>
<td>8 (26.7%)</td>
<td>17 (56.7%)</td>
<td>10 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>1 (3.3%)</td>
<td>7 (23.3%)</td>
<td>17 (56.7%)</td>
<td>5 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>3 (10.0%)</td>
<td>13 (43.3%)</td>
<td>8 (26.7%)</td>
<td>4 (13.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: N, number of patients in group; %, percentage of patients in group.
Summary: Zulresso is a new version of old drugs, has a very similar mechanism of action as benzodiazepines and barbiturates and progesterone, and is largely inferior to methods already available. This indicates the cost cannot be justified by:

1) novelty of the molecule
2) novelty of the disease being treated
3) effectiveness for the disease being treated
4) extra safety of the method being used

It is reasonable, then, that many advocacy groups expressed outrage at the initial cost of the drug.

So, why does it cost so much?

Hypothesis: Zulresso is the only commercially viable drug to enter into the PPD therapy space
The true cost of new drug development: every indication needs a phase 3 clinical trial demonstrating efficacy

- Brexanolone (Zulresso) has undergone 13 distinct clinical trials with several add-ons.
  - Phase 2:
    - IV for postpartum depression (completed)
    - IV for super-refractory status epilepticus (completed)
    - IV for essential tremor (completed, EFFECTIVE)
    - IV for Parkinson's disease (ongoing)
    - IV for major depressive disorder (ongoing)
  - Phase 3:
    - IV for super-refractory status epilepticus (completed, not effective)
    - IV for postpartum depression (completed, EFFECTIVE)
    - IV for postpartum depression in adolescent females (ongoing)
    - Oral for major depressive disorder (ongoing)
Most drugs fail because of a lack of demonstrable clinical efficacy (phase 2+), not lack of safety or physiologic response.
FROM THE ANALYST’S COUCH

Phase II and phase III failures: 2013–2015

Richard K. Harrison

Figure 1 | Reasons for clinical trial failures 2013–2015. The pie charts illustrate the reason for failure for phase II and phase III trials for which a reason for failure was reported for all 174 clinical trials (part a), according to therapeutic area (part b), in all therapy areas for phase II only (part c) and in all therapy areas for phase III only (part d). Data are from Thomson Reuters and Drugs of Today (©Prous Science S.A.).
Figure 2 | Recent trends in clinical trial failures. 

**a** | The combined percentage of phase II and phase III clinical trial failures in the three periods indicated by the colour codes, subdivided according to therapeutic area.

**b** | Reasons for failure in phase II clinical trials.

**c** | Reasons for failure in phase III clinical trials. In each panel, the total data for each colour-coded time period represent 100% of the reported failures in that time period. Data are from Thomson Reuters and Drugs of Today (©Prous Science S.A.).
A disproportionate number of drugs which do make it to market, target disease indications with known mechanisms. Zulresso, though not reported as such, fits this category as a GABA-A receptor modulator.
Most companies do try new mechanisms, but rarely retry them.

**Figure 6 | Ongoing projects for the repeatedly validated and continually unvalidated mechanism–indication pairs.**

**a** | Ongoing projects for repeatedly validated mechanisms (defined as those that have ≥5 successful projects at or beyond pre-registration status) constitute 8% of total ongoing projects in the same indications, with those targeting validated mechanisms (those that have at least one successful project) constituting ~18% of the total for these indications. So, >80% of projects in these indications are targeting unproven — and thus potentially riskier — mechanisms. **b** | Ongoing projects for continually unvalidated mechanisms (defined as those that have ≥5 discontinued projects) constitute 8% of total ongoing projects in those same indications. These projects probably have a lower chance of success later in development.
A small number of ‘highly-hypothesized’ unvalidated drug targets receive most of the attention for new drug trials.
The R&D necessary to demonstrate efficacy only rarely results in approval. Many clinical trials must be performed: even then, the drug may not make money

- Zulresso was first used clinically in the summer of 2019. Thus, the Sage Therapeutics Earnings Call to Investor (published Nov 13, 2019 on investor.sagerx.com) gives an indication of how much revenue it will pull in, compared to how much it spends on Earnings.

- Per Chief Financial Officer, Kimi Iguchi:

  "Starting with our balance sheet, we ended the third quarter with $1.1 billion in cash, cash equivalents, restricted cash, and marketable securities compared with $925.1 million at the beginning of the year. Our cash on hand keeps us in a strong financial position as we work to deliver upcoming milestones across all three of our brain health franchises. Turning now to the rest of our financial results for the third quarter. Revenues were $3.6 million in the third quarter, which consisted of $1.5 million of ZULRESSO net product revenue and a $2.1 million in expense reimbursement related to our collaboration with Shionogi [a Japanese pharmaceutical company which is collaborating to test oral brexanolone and bought the patent rights]. For comparison, there were no revenues in the third quarter of 2018. [...] We now have five clinical candidates across three franchises. As a result, our R&D expense increased to $102 million in the third quarter compared to $75 million for the same period of 2018."
Zulresso was a tactic to get past FDA efficacy requirements and reassure shareholders

- Sales of Zulresso resulted in $1.5 million returned over Q3 2019. Even 50x those sales will not negate the $100 million R&D budget.

- However, since Zulresso was considered such a success, the FDA apparently has decided to relax concepts of efficacy. Per a Q&A session later in the phone call:

  [investor]: “Hi. Thank you. This is [investor]. A quick question. For 217, how important do you believe sustained clinical benefit is to physicians and regulators out to day 42? Thank you very much.”

  Jeff Jonas: “ [...] The other point I’d like to make is that, if you look at our data, the drug so far has worked very rapidly. So, we believe it will always have a role in treating patients where rapid resolution of symptoms is desirable. We think this is one of the great options that we might be able to offer the field if this drug is approved, which is rapid onset of action without chronic pharmacotherapy, and has also been used as an adjuvant in about a third of our patients. [...]”

  Steve Kanes: “With regard to sort of regulatory treatment, we look at how the FDA viewed the data from the ZULRESSO development program. And in that case, what was important to the FDA was when patients got better, they remain well. It has nothing to do with statistical significance out through a month or more after the treatment, it was to the patients bounce back with their symptoms as soon as the treatment stops or do they overall stay well and have continued benefits. That's the important piece of it. That's the pattern that we've seen with 217 in our two prior trials and what we think, as Jeff has described, represents a true change in paradigm for treatment of patients.”
Shareholder investment and patent licensing are the primary engine for maintaining solvency for pharmaceuticals

- Per the Q3 earnings report, Sage Therapeutics raised $175 million from the beginning of the year. Only 2.5% of this was from sales of Zulresso.

- In 2018, Sage reached an agreement to license the oral form of Zulresso to Shionogi, to test for treatment of depression.
  - Sage received $90 million upfront, will receive up to $485 million as testing milestones are met by Shionogi, and tiered royalties.
  - The royalties received from the testing phase, $2.1 million, already outpace those of the sale of the commercially available drug.
Fears that drugs will not be labeled as effective by the FDA are a primary driver of shareholder action

- In March 2016 the research-oriented Wall Street investment firm Kerrisdale Capital purchased Sage stocks in the short position
- They then published an article titled “Overhyped lead-drug headed for failure” and discussed how Zulresso will never differentiate itself from midazolam, propofol, pentobarbital, or ketamine for status epilepticus, because they all work by the same mechanism (they were correct, of course, as Zulresso ultimately failed phase 3 trials for status epilepticus)
  - In response to this, Sage stock value dropped by 15% within a single day
  - This prompted Rosen Law Firm to start a class action lawsuit against Sage for materially false and misleading statements about Zulresso’s capacities in order to attract investment
- However, by July 2016, Sage was able to publish highly convincing open-label phase 2 trial results on the use of post-partum depression (a disease with no previous FDA-approved treatment, and hence can be compared solely to placebo)
  - Sage stock price skyrocketed by 40% by the end of the day
  - The class action lawsuit is no longer being pursued
Zulresso costs so much because it was necessary to show some sort of revenue stream that convinces investors and patent licensees to continue to interact with Sage. However, it does NOT generate substantial revenue in of itself. Given that so many new drugs are in similar situations, it appears that this may undergird most drug novel drug costs – to prove to investors it will eventually be commercially viable.

Currently, only the Sage model seems to produce commercially viable drugs. It is a startup company, but run by industry insiders (the CEO Jeff Jonas previously worked as chief medical officer for Pfizer, and the scientific founder Steven Paul worked in leadership roles for the NIMH, NIH, FDA, Eli Lilly, and several other pharmaceutical companies). It is managing massive financial bets, currently carrying (per the Q3 call) a $900 million dollar deficit. Its biggest source of revenue is patent licensing on a different drug that now is much more likely to reach FDA approval. Sage was only able to attain this success by marketing a drug that barely squeaks by efficacy requirements, choosing a very specific, non-traditional kind of efficacy end-point, is able to get a drug past the FDA approval process.

**Question:** What element of this process may be artificially increasing the barrier to entry for a drug to be commercially viable, such that all of the costs (from R&D to cost of a new drug to patient) are so inflated?

**Hypothesis:** The FDA requirement that new drugs show efficacy is not resulting in effective drugs (hence Zulresso), but is artificially restricting the market and increasing costs
Discussion and Evidence
The FDA efficacy requirement – a reconsideration

- The Kefauver-Harris amendment of 1962 gave the FDA the authority to approve new drugs based on efficacy
  - This, ironically, was passed in response to the thalidomide tragedy, where Dr. Frances Kelsey, a medical reviewer for the FDA, had successfully prevented it from being marketed in the U.S. from concerns for safety. The drug was very effective, but had serious side effects (polyneuropathy and phocomelia in pregnant mothers)

- At the same time, FDA safety methods were altered to focus on good manufacturing processes and plant inspections, and a rejection of a previous measure to allow batch testing of pharmaceuticals
Ineffective and safe drugs routinely get FDA approval

- Zulresso is a perfect example of this – while there may be some validity to the short-term restoration of symptoms, in no world is a $34,000 treatment that lasts for a few days considered effective.

- Other examples: phenylephrine for cold symptoms, cholestyramine for cholesterol, donepezil and memantine for Alzheimers, buspirone for anxiety.
Effective and safe drugs may not be receiving FDA approval

- MDMA-assisted psychotherapy for PTSD was shown to be highly effective before it was criminalized in 1984.
- The FDA refused to give it investigational drug status despite 5 applications between 1984 to 2011; it now is in phase 3 trials.
Effective and safe drugs may not be receiving FDA approval

- The Nature Reviews Drug Discovery article demonstrates that most drugs with unique mechanisms which do not make it past phase 3, often do not get tried for any other indication: There is a veritable graveyard of potential drugs not available to the market for testing that

- Dr. Matthew Lewin, an MD/PhD graduate of McGovern Medical School, has created a companies focused on reviving a phospholipase A2 inhibitor developed, then abandoned, by Eli Lilly as a treatment for sepsis in the 1990s. His work shows it is a panacea for snake bite venom, but his company, Ophirex, is currently repeating all of the FDA investigational drug status steps..
Unsafe medications are passing the FDA approval process

- Ranitidine is a well-known stomach acid reducer – however, it breaks down in the stomach into an FDA-banned carcinogen contaminent, NDMA (N-nitrosodimethylamine)
  - An independent pharmacy which batch-tests pills in physiologic conditions as per FDA recommendations, Valisure, has published these results in October 2019 (supported by data published in 2016: Zeng, T. & Mitch, W. A. Oral intake of ranitidine increases urinary excretion of N-nitrosodimethylamine. Carcinogenesis 37, 625–634 (2016)
  - The FDA has yet to recommend cessation of ranitidine, and so far has only reported voluntary withdrawals
Generic drugs manufactured internationally are not sufficiently monitored for good manufacturing practices – efficacy and safety have declined as a result of ineffective FDA oversight

- The mere act of switching from brand name to generic is associated with a statistically significant increase in risk of developing seizures, more than switching from one brand to another

- International manufacturers sell faulty products: many instances of outright fraud and faking of data by Indian pharmaceutical manufactureres was demosntrated by investigative journalist Katherine Eban, in her book Bottle of Lies (2019).
  - The U.S. government purchased over $1 billion dollars of anti-HIV medications from Ranbaxy in the early 2000s to distribute to AIDS stricken regions, despite repeated reports that they did not contain active ingredients. These drugs were DA approved.
  - The generic drug Lipitor, also sold by Ranbaxy, was shown to have glass shards in millions of pills tested

- No meaningful alteration in the method of oversight for quality assurance and safety has been adopted by the FDA to this point in response to these concerns.
Conclusion
A proposal: drop the efficacy requirement and focus on safety and data transparency

- Pharmaceutical companies live and die by FDA-approval; even the hint that their drug will not be effective can send stocks plummeting
- FDA approval is not a sure guarantee of efficacy: yet it results in restriction of the market for ‘FDA-approved’ treatments such as Zulresso
  - This is a major excuse (and in this case, burden) for insurance companies to make coverage decisions. The same is true of medical providers and government healthcare
  - Yet, effective and safe medications sometimes don’t make it to the market, but ineffective and safe, and effective and unsafe, medications do
- **First Proposal:** the FDA should continue to require quires, but no longer restrict sale of pharmaceuticals based upon efficacy
- **Second Proposal:** an emphasis on increasing access to information about new drugs, especially with regards to true novelty, will help the market decide what sorts of prices are truly worth it
  - Hearing “the first FDA-approved drug for post-partum depression” is very different from “a derivative of a 1950s anesthetic agent which acts just like Xanax is being marketed for post-partum depression”
  - Another method is to adopt the NIH Grant review process, with a panel of experts who can score drugs based off of a variety of categories including novelty, efficacy from current data, abuse potential, side effects, excipients, etc.
    - This score must be published will all drug-related materials. It will not determine whether it can be commercially sold, but it will provide a very useful “value signal” much like safety ratings for cars have done.
- **Third Proposal:** with reduced costs by the FDA spent on evaluating efficacy, more effort can be spent on rigorously evaluating safety of drugs, including adopting a batch sampling process similar to that used by Valisure
A final note

- I do not think any actor I have described above has acted with negligence or malfiesance.
- I believe Sage Therapeutics is pursuing this mechanism to finally validate the hormone-withdrawal theory of depression. I think the pricing decision was based off of the intense market pressures and change of regulatory destruction.
- I also believe the FDA is pursuing a noble goal and has been very effective in many ways. I think that the task it has been handed is too difficult to accomplish as there are three conflicting political pressures:
  - Only allow safe drugs on the market
  - Only allow effective drugs on the market
  - Reduce the cost of drugs
- It becomes impossible to balance these three to the satisfaction of all stakeholders. Moving the responsibility to determine efficacy (i.e. whether a drug should be used) to the academic research community and physicians and patients at large, is a way to shift this burden and, potentially, allow the other two to be optimized through FDA action.