

# Low Dose Risperidone Every 3.8 Hours: Superior Efficacy In Treatment of Bipolar Disorders

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## Research Article

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# Abstract

**Background:** This paper presents a previously unpublished Bipolar Disorder treatment using low-dose Risperidone that gives superior-efficacy, prevents overmedication, and prevents medication-induced anxiety and irritability. Standardized other Bipolar Disorder treatments have a failure rate of 82% to 87.1%. When dropouts and poor adherence are combined, only 12.9% to 18% of Bipolar patients adhere to medications within three years. Self-defensive providers primarily blame Bipolar patients for treatment failures. When that bias is removed, failure is due to overmedication and anxiety and irritability caused by medications. This paper shows the neurobiochemical processes that cause those problems. Published prescription-guidelines recommend Risperidone in high amounts that intentionally activate its 9-Hydroxyrisperidone metabolite under auspices that it is virtually the same as Risperidone and lasts for 24 hours. In truth, however, the beneficial Risperidone chemical lasts for four hours and 9-Hydroxyrisperidone agonizes Bipolar-toxic Serotonin. Low-dose Risperidone neutralizes 9-Hydroxyrisperidone.

**Methods:** Low doses of Risperidone were calculated to be therapeutic amounts without causing overmedication, anxiety, and irritability. Doses were calculated to metabolize low plasma concentrations of 9-Hydroxyrisperidone that stay below the neural-activation threshold level. Four-hour-duration low doses of Risperidone were administered every 3.8 hours.

**Results:** 3.8-hour dosing sustained steady benefits by overlapping 15-minute efficacy-onset with the 15-minute termination of each previous dose. Steady transitions between doses and five administrations per day gave therapeutic efficacy for 16 hours. Taking dose #5 at bedtime gave improved sleep.

**Conclusions:** Low doses of Risperidone activate its therapeutic benefits while neutralizing Bipolar-toxic Paliperidone. Low-dose Risperidone every 3.8 hours maintains stability with room for adding occasional extra doses to control exacerbations of symptoms. This study provides a new biochemistry-based Bipolar Disorder treatment that is vitally needed because the failure rate of traditional treatments is too high. Traditional treatments and research are guided by commercial drug manufacturers' recommendations and data. Traditional treatment dropout and non-adherence rates attest to the immediate need for this paper's new paradigm of analytic neurobiochemistry.

## Definitions Of Technical Terms

**Activation:** Minimum serum concentration that initiates/triggers synaptic responses.

**threshold :** Below the threshold, a medication is biochemically *inert* or *inactive*. At or above the threshold, a medication is biochemically *active* or *activated*. This is strictly biochemical. It does not imply *noticeable, clinical, or primary effects*.)

**Active moiety:** A manufacturer-promoted widely accepted false concept in Risperidone product inserts that says Risperidone and Paliperidone are a single entity. The misleading marketing gimmick claims (a)

4-hour-duration Risperidone has the 24-hour duration of Paliperidone and (b) 24-hour lesser-efficacy-Paliperidone has the greater-efficacy of 4-hour Risperidone.

**Manufacturer:** Johnson & Johnson (J&J) invented, owns rights, produces, and markets Risperdal/Risperidone and Invega/ Paliperidone. Product labels and other product literature are often printed and published under the name *Janssen Laboratories* or *Janssen*, a J&J subsidiary owned and controlled by J&J. Other manufacturers also produce and sell generic Risperidone and Paliperidone.

**Paliperidone:** Chemical name *9-Hydroxyrisperidone* was first discovered as a chemical metabolite of Risperidone. Paliperidone has been isolated and is manufactured separately by J&J as an Antipsychotic medication under the brand name *Invega*. The Risperdal product insert says the half-life of Paliperidone is 21 hours. The Invega insert says 23 hours.

**Risperdal:** “Risperdal” has two definitions: (a) J&J and Janssen’s brand name for Risperidone. (b) An *active moiety* combination of Risperidone-efficacy and Paliperidone-efficacy.

**Risperidone:** Chemical name: *Risperidone*. Risperidone is the scientific name of a specific chemical compound. The reported half-life varies across studies from 2.8 to 3.4 hours. Efficacy and biochemical duration are generally agreed to be 4 hours. In this paper the names *Risperidone*, *chemical-Risperidone*, and *chem-Risperidone* are used for the specific Risperidone chemical compound as differentiated from (a) the *metabolization* process, (b) metabolites such as *Paliperidone*, (c) *Risperdal* (see definition above), and (d) an ostensive *active moiety* combination of Risperidone and Paliperidone.

## Background

This paper presents a groundbreaking and vastly superior new paradigm for treating Bipolar Disorders. This author is unaware of any other studies of the neurobiochemistry processes and Bipolar Disorder treatment methods presented in this paper. Risperidone is used in the Mental Health profession as a major mood stabilizer and as an antipsychotic. Risperidone has two main components: (1) a chemical with the scientific name *Risperidone* and (2) *9-Hydroxyrisperidone*, an antipsychotic-metabolite of Risperidone also known as *Paliperidone*. Risperidone was FDA approved for Bipolar Disorder treatment in 1993 under the brand name *Risperdal*. Paliperidone is not FDA-approved for Bipolar Disorder treatment. The FDA rejected Paliperidone-Invega for Bipolar treatment in 2006, 2009, and 2011. This is the first paper known to this author to analyze the Bipolar-toxic properties of Paliperidone. This is the first paper known to this author to present a vastly superior method of Bipolar Disorder treatment that uses low-dose Risperidone every 3.8 hours and neutralizes Bipolar-toxic Paliperidone.

51.5 million adults in the United States (20.6%) reportedly experienced Mental Health problems during 2019. Forty-six million people worldwide reportedly had Bipolar Disorders during 2018 with a reported 2.8% prevalence of Bipolar Disorders in the USA during 2019. Common Bipolar Disorder treatments combine antiepileptics such as Valproic Acid and antipsychotics such as Risperidone. Risperidone is a 4-hour chemical that metabolizes into 24-hour Paliperidone. This is the first research paper to strictly

differentiate between Risperidone, Paliperidone, and an ostensive *active moiety*. Standard daily Risperidone of 2mg to 8mg or more metabolizes activation-amounts of Paliperidone. Little known laboratory studies show Paliperidone increases Prolactin and Serotonin. Standard-dose Risperidone exceeds effective small amounts by 400% to 1600%, causing unnecessary Risperidone overmedication for four hours followed by 21 hours of harmful Serotonin agonism by Paliperidone.

To the best knowledge of this author this is the first research paper to address those issues. To the best knowledge of this author this is the first research paper to overcome those issues by developing a superior new Bipolar-treatment with low-dose Risperidone every 3.8 hours. Low doses of 0.25 mg, 0.5mg, 0.75mg, and 1.0 mg activate the benefits of Risperidone without activating Paliperidone. Administration every 3.8 hours sustains efficacy by overlapping 15-20-minute efficacy-termination of one dose and 15-20-minute onset of the next dose. This new method is overtly superior to the universally accepted 30-year standard. Neurobiochemistry data in this paper is from a review of scientific literature. Case study information is from the author's outpatient treatment experiences with Bipolar Disorder patients. Drug-manufacturer information is from a review of history literature.

### Risperidone reduces Dopamine and Serotonin

Bipolar Disorders have a neurobiochemical trait of receptor-synapses that absorb excessive amounts of Dopamine and Serotonin. This over-activates the nervous system, e.g., the brain. Medications that reduce synaptic-absorption of Serotonin and Dopamine can calm and stabilize Bipolar nerves and brains. Reductions can occur through antagonism of receptors, antagonism of natural production of Dopamine and Serotonin, antagonism of transporter-cell bonding and production, and increased reuptake. Low serum concentrations of Risperidone can reduce synaptic absorption of Dopamine and Serotonin. Increased serum concentrations can further decrease absorption of Dopamine and Serotonin.

### Two definitions of "Risperidone"

The word "Risperidone" has two definitions: 1) In scientific chemistry "Risperidone" is the scientific name, or *chemical name*, of a specific 4-hour duration chemical. Its unique chemical-identification number (CID) is 5073. Its unique chemical structure is  $C_{23}H_{27}FN_4O_2$ . In scientific chemistry it is distinctly differentiated from its metabolite chemicals. 2) In commercial drug marketing "Risperidone" is the generic name of the brand name medication "Risperdal" that is marketed as an inextricable combination (*active-moiety*) of the name-ingredient and it's 23-to-26-hour duration metabolite Paliperidone (9-Hydroxyrisperidone). This paper avoids confusion by using "chemical-Risperidone" as a topic or paragraph lead-in for the scientific chemistry definition.

## Onset-time, half-life, and efficacy-duration

Chemical-Risperidone has a short half-life of 2.8 to 3.5-hours depending on which source is being cited<sup>1, 2, 3, 4</sup>. A study with 19 pediatric inpatients [2] showed a half-life of 3.0 hours. The study showed Risperidone plasma levels dropped to dose-administration levels (horizontal red line in [Figure 1](#) below) at 4 hours then dropped below dose-administration levels. Adult patients at this author's Mental Health clinic consistently reported the effects of Risperidone fade noticeably between 3.9 and 4 hours and end at about 4 hours. Patients' reports were consistent with household members' reports, this author's clinical observations, and the above study. The plasma concentration drops below the dose-administration level and efficacy ends at about 4 hours. This author's patients also consistently reported that beneficial effects of Risperidone are noticeable 15 to 20 minutes after ingestion. This was also consistently reported by patients' household members and was consistently observed by this author hundreds of times.

### Efficacy duration is independent of dose-amount, length of use, and adjunctive medications

Participants in the above study were 19 pediatric inpatients ages 4 to 16 of several diagnostic categories. All were on established maintenance Risperidone therapy twice per day prior to and during the study. Doses ranged from 0.25 mg BID to 2.5 mg BID. Four participants were on Risperidone monotherapy. Fifteen participants were taking concurrent medications with a wide range of amounts wherein some took 10 times more than others. Among the participants the half-life and duration of Risperidone were constant regardless of dose-amount, length of use, type and amount of co-medication, diagnosis, age, and gender. Research studies consistently show that among the vast majority of people Risperidone metabolizes completely into other chemicals at or very near the 4-hour mark.

### 15-20-minute onset-time, moot half-life, and 4-hour duration

Onset. Several research studies report a median T-max of 1-hour and a dose dependent C-max [8]. This is the first paper this author knows of that includes patient-reported efficacy onset time of chemical-Risperidone. This author's Bipolar Disorder treatment patients and their participating household members consistently reported an onset-time of 15 to 20 minutes after pill ingestion. The author also consistently observed the 15-to-20-minute onset-time during clinical therapy sessions. The short onset time is an important component of the Bipolar Disorder treatment method presented in this paper.

Half-life. The traditional definition of "half-life" states that after five half-lives a chemical is 94% eliminated and after six half-lives it is 98% eliminated. The half-life of Risperidone is reportedly 2.8 hours, 3 hours, 3.2 hours, or 3.4-hours (the mean among these reports is 3.1 hours) depending on which source is cited (4, 6, 7, 8). On one hand, given the reported the shortness of the half-life, a 36-minute difference among reports is considerable. On the other hand, this is the first research paper that the author knows of to show that the traditional concept of "half-life" is moot for Risperidone. The median reported half-life is 3.1 hours, whereby it would be 98% eliminated only after 18.6 hours. However, what actually happens is this:

1. On one hand, a 3.1-hour “half-life” is too long. Four hours after intake the chemical structure of Risperidone metabolizes into several other chemicals whereby the chemical structure of Risperidone becomes disassembled and no longer exists. Risperidone has a 4-hour duration, not a 3.1-hour “half-life”.
2. On the other hand, a 3.1-hour “half-life” is too short. The manufacturer has cleverly convinced everyone (other than this author) that Risperidone is combined with a metabolite with a half-life of 20 to 25 hours. Everyone (except this author) dogmatically believes “Risperidone and Paliperidone” are 98% eliminated at 120 to 180 hours although everyone also believes Risperidone has a 3.1-hour half-life.

The reports of a 2.8- to 3.4-hour half-life and a 20- to 25-hour half-life are not valid predictors of Risperidone elimination. The short-half-life reports and the long-half-life reports misrepresent the 4-hour coherence and efficacy of Risperidone. The traditional definition of “half-life” is irrelevant for Risperidone. The applicable time-measure for Risperidone is *duration*.

*Duration*: Chemical-Risperidone *duration* regards the starting point and ending point of three interrelated factors: 1) specific chemical-structure, 2) chemical-specific neural responses, and 3) chemical-specific clinical efficacy. C-max and T-max occur at 1-hour. Plasma concentration then decreases for three hours to the initial intake level. When an intake level is above zero due to a previous dose, the level drops below intake to zero about 10 minutes after hour-4 (8). All of the author’s Bipolar Disorder patients reported that noticeable effects begin 15-20 minutes after dose-intake and effects start fading about five minutes before they end at about hour-4 (see [Figure 2](#) below).

### Superior responses from a lower blood level

Oral tablet Risperidone is more clinically potent than Paliperidone. This is partially due to bioavailability of 68% versus 28% respectively. The difference in bioavailabilities is largely due to a higher Paliperidone affinity for efflux protein Pgp (ABCB1). This affinity decreases brain exposure to medications by reducing brain tissue permeability [11]. A significantly higher percent of blood-borne Risperidone passes through the blood-brain barrier tissues to enter the brain. The brain-absorption of higher quantities of Risperidone enables lesser amounts of medication to induce superior efficacy. The good bioavailability of Risperidone might be advantageous for any diagnostic category of patients who use antipsychotics. It is particularly advantageous for patients with Bipolar Disorders. Bipolar Disorders cause Dopamine and Serotonin to over-activate the brain and the nervous system. Effective antipsychotics calm the brain and nerves by reducing Dopamine and Serotonin absorption. Reduction is done by receptor inhibition, transporter-cell inhibition, and inhibition of production.

Risperidone is a benzisoxazole derivative. It is a selective monoaminergic antagonist with a high affinity for binding to and occupying Serotonin and Dopamine synaptic receptors. It has a ten to twenty times higher affinity for 5-HT<sub>2A</sub> receptors than for D<sub>2</sub> receptors (8). It significantly decreases both Dopamine and Serotonin absorption. It also inhibits absorption in other ways. A laboratory investigation of

Risperidone vs. Paliperidone neural-activation functions and neural-responses spoke of “concentrations of paliperidone (3  $\mu\text{M}$ ) and risperidone (1  $\mu\text{M}$ )” that were “obtained from concentration-response curves for signaling responses at 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors.” The investigation found that three times less Risperidone than Paliperidone induced neural responses [6].

In the laboratory investigation serum concentrations for neural responses had a 1-to-3 ratio of Risperidone-to-Paliperidone. Neural responses to Paliperidone differed from responses to Risperidone. 1  $\mu\text{M}$  of Risperidone significantly reduced the release and functions of Serotonin transporter Arachidonic acid (AA). A three times higher amount of 3  $\mu\text{M}$  Paliperidone increased AA sensitivity causing AA transporter cells to gather increased amounts of Serotonin and carry it to receptors. Researchers found that the differing effects on AA significantly impacted the amounts of Serotonin that were absorbed by 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors. Risperidone reduced the number of AA transporters and decreased the amount of Serotonin that transporter cells brought to synaptic receptors. By allowing less incoming Serotonin the amount of Serotonin that was absorbed by receptors decreased. Paliperidone made AA transporters more efficient. By not reducing their number an increased amount of Serotonin was brought to synaptic receptors. Thereby the amount of Serotonin that was absorbed by synaptic receptors increased (see [Figure 3](#) and [Figure 4](#) below).

Odou, et al found that in a response in 5-HT<sub>2C</sub> receptors, Risperidone was an inverse agonist and reduced basal AA release by  $14 \pm 2\%$ . By contrast, Paliperidone reduced basal AA release by only  $0.5 \pm 8\%$  and behaved as an agonist. In 5-HT<sub>2A</sub> receptors only Risperidone significantly reduced AA release ( $17 \pm 4\%$ ). Another comparative study found Risperidone occupied 17% more D<sub>2</sub>-Dopamine receptors and 28.2% more 5-HT<sub>2A</sub>-Serotonin receptors. The reported D<sub>2</sub>-receptor affinity of Paliperidone was three times lower than that of Risperidone. Risperidone occupied a greater number of D<sub>2</sub> and 5-HT<sub>2A</sub> receptors. The occupied receptors were less able to absorb Dopamine and Serotonin. [12]. Activation of neural response requires three times higher serum concentrations of Paliperidone and the resulting Paliperidone responses are harmful to Bipolar Disorders.

## Methods

### 1) Aim of this study

This paper is an independent Humanitarian work that brings the world a critically needed paradigm of scientific neurobiochemistry to safely and effectively help people who have a Bipolar Disorder.

### 2) Design of this study

This paper is based on data found online in approximately 120 existing documents (see [Description of Materials Used in This Study](#) below).

### 3) Setting of this study

This author owns and operates a one-person private practice Mental Health clinic that is not used for experimental research. This author's research consists of extensively gathering and analyzing information documents and research studies found on the internet.

#### 4) Characteristics of study participants

Four of this author's Bipolar Disorder clinical patients and two of their household family members signed consent forms allowing medication-pertinent treatment information to be mentioned in this paper. These were not experiment subjects. They did not actively participate in this study.

#### 5) Description of materials used in this study

Internet searches gathered a wide range of scientific research documents, prescription guidelines, drug product package inserts, letters and other documents exchanged back and forth between the FDA and the manufacturer, FDA documents evaluating the manufacturer's Approval Application research reports, clinical efficacy research studies, laboratory in-vivo investigations of chemical properties and interactions.

#### 6) Description of the processes used in this study

See #5 above

#### 7) Interventions used in this study

No experimental interventions were used in this study.

#### 8) Comparisons used in this study

Risperidone was compared to Paliperidone vis á vis review and analysis of data in existing documents found online regarding dose-related clinical efficacy, duration of clinical efficacy, chemical structure, duration of chemical structure, neurobiochemical properties, neurobiochemical actions and potentials, histories of product development, and histories of FDA approvals

#### 9) Type of statistical analysis used in this study

Basic Algebra was used for calculating Risperidone dose-amounts, plasma concentrations, and activation thresholds.

#### **Differential-activation: Activating Risperidone while neutralizing Paliperidone**

The neuropsychiatric benefits of Risperidone can be activated without neural responses to Paliperidone. To the best knowledge of this author this is the first research paper regarding differential-activation of Risperidone and Paliperidone. This is the first research paper to show differential-activation is possible. This research paper also is the first to present a treatment method that activates the benefits of

Risperidone without activating responses to Paliperidone. This topic is new and critically important for the treatment for Bipolar Disorders.

Many people in the Medical and Research Communities are aware that Serotonin destabilizes Bipolar Disorders and that Risperidone is a Serotonin antagonist. The vast majority of Medical and Research people are unaware that metabolite Paliperidone is a Serotonin agonist that needs to be neutralized for safe and effective treatment of Bipolar Disorders. Key factors for accomplishing this critically necessary *differential-activation* include:

- A) At about 4-hours Risperidone metabolizes into other chemicals including Paliperidone.
- B) Risperidone efficacy occurs at low serum concentrations [12] that metabolize inactive small amounts of Paliperidone [6].
- C) Risperidone metabolizes into 77.35% of its volume in Paliperidone, yielding 22.65% less Paliperidone than Risperidone [9].
- D) The activation-threshold serum concentration of Paliperidone is three times higher than activation-threshold of Risperidone [6].

To the best awareness of this author, this is the first paper to show that it is beneficial to activate the psychoactive properties of chemical-Risperidone while not activating the psychoactive properties of Paliperidone. To the best awareness of this author, this is the first paper to show that it is possible to activate to activate the psychoactive properties of chemical-Risperidone while not activating the psychoactive properties of Paliperidone. To the best awareness of this author, this is the first paper to show how to activate the psychoactive properties of chemical-Risperidone while not activating the psychoactive properties of Paliperidone. When providing clinical treatment for Bipolar Disorders it is critical to differentially activate the former and not the latter. Chemical-Risperidone is a powerful Serotonin and Dopamine antagonist. Paliperidone is a harmful Serotonin agonist and a weak Dopamine antagonist. Key factors for calculating a *differential-activation* regimen include:

- 1) Efficacy of Risperidone occurs at low serum concentrations.
- 2) At about 4-hours Risperidone metabolizes into other chemicals.
- 3) The metabolites are inert other than Paliperidone.
- 4) The serum concentration activation-threshold of Paliperidone is three times higher than the serum concentration activation-threshold of Risperidone [6].
- 5) Risperidone metabolizes into 77.35% of its volume in Paliperidone, yielding 22.65% less Paliperidone than Risperidone [2].

An *active-moiety* research article by Odou et al studied Paliperidone serum concentrations in relationship to clinical-efficacy. The authors wrote, “Statistical analysis revealed a significant increase in efficacy when the serum concentration of active drug was between 25 and 150 µg/L...” This author marked the level of clinical efficacy from Paliperidone 25 µg/L with vertical red line in [Figure 5](#) below. [Figure 6](#) below shows “*active-moiety*” (Paliperidone) plasma concentration levels and corresponding Risperidone dose-amounts per day.

On [Graph F](#) this author marked 25 µg/L with a horizontal green line that intersects the Curve-1 efficacy-mean at the 0.051 mg/kg point. This is equivalent to 4.627 mg for a 200-pound person, 3.933 mg for 170-pounds, 3.47 mg for 150-lbs, 3.0073 mg for 130-lbs, 2.6603 mg for 115-lbs, or 2.3133 mg for 100-lbs. This yields Paliperidone 25 µg/L and the above-mentioned significant increase in clinical efficacy [13].

The phrase “significant *increase* in efficacy” said minimal efficacy occurred at a lower concentration than 25 µg/L. This author re-analyzed the data and found minimal Paliperidone efficacy occurred at 23.9 µg/L (see [Figure 7](#) below). This corresponds with Risperidone .05 mg/kg, equivalent to 4.5 mg for a 200-lb person, 3.75 mg for 170-lbs, 3.5 mg for 150-lbs, 3 mg for 130-lbs, 2.5 mg for 115-lbs, or 2.25 mg for a 100-lb person (see [Figure 8](#) below) [13].

The above study listed mg/kg dosages per body weight. The average weight of USA males is 197.9 pounds [14] and 170.6 pounds for females [15] (see [Figure 9](#) and [Figure 10](#) below). According to data from the above study, minimum clinical efficacy of Paliperidone requires a Paliperidone serum concentration of 23.9 µg/L. That requires Risperidone daily dose-amounts of 4.48 mg for average-weight males and 3.87 mg for average-weight females [16] (see [Figure 9a](#) and [Figure 10a](#) below).

The 4.48 mg and 3.87 mg dose-amounts were for average-weight USA Americans. Such persons are significantly overweight. Their dose-amounts may be too high for persons of healthier weight. In order to find dose-amounts for persons of healthier weight, this author used the weight-range means for average height males (5’9”, 156.66 pounds) and females (5’4”, 131.33 pounds). The calculated daily dose-amount for healthier-weight men is 3.55 mg and 2.98 mg for healthier-weight women (see [Figure 11](#), [Figure 11a](#), [Figure 12](#), and [Figure 12a](#) below) [12, 13].

The calculated dose-amounts for healthier-weight and average-weight USA Americans correspond to the Paliperidone serum concentration that was associated with minimal clinical efficacy on CG1<sub>2</sub> test-scores. The clinical efficacy dose-amounts and serum concentration seem to affirm a synaptic-activation threshold but biochemical data is needed in order to correctly identify a synaptic threshold and dosage parameters.

#### Factors for calculating dose-amounts that activate Risperidone without activating Paliperidone

Factors for calculating appropriate dose-amounts include but are not limited to:

1. The appropriate Risperdal/Risperidone doses are 3.2265 times less than doses that activate Paliperidone. This is a biochemical ratio with two inherent properties:
  1. The needed amount of Risperidone serum concentration is three times less than the amount of Paliperidone serum concentration that affects synaptic functions<sup>6</sup>.
  2. Risperidone metabolizes into 22.65% less Paliperidone than the original amount of Risperidone<sup>2</sup>.
2. Risperidone has an onset time of 15-20 minutes, a half-life of 3.2-3.5 hours, and its clinical efficacy and chemical-structure end at 4 hours [2].

Steady efficacy requires a steady serum concentration that requires taking Risperidone every 3.8 hours. Due to the frequency, routine small doses plus small extra doses taken as needed provide steady efficacy without overmedicating the patient and without activating Paliperidone. When a patient is starting Risperidone (or any psychoactive medication), introduce it slowly in a way that minimizes and/or prevents grogginess. Keep in mind that medication-grogginess is a tiredness of the body, muddled/slow thinking, and flat or irritable emotions. Medication-grogginess is the leading cause of poor adherence and quitting treatment among Bipolar Disorder patients. The new treatment paradigm in this paper prevents medication-grogginess.

#### Calculating *differential-activation* dose-amounts

*Differential-activation* is defined herein as an induction of neural responses to Risperidone without an induction of neural responses to Paliperidone. *Differential-activation* requires maintaining Paliperidone at below the serum concentration that induces neural responses to Paliperidone. The preceding re-analyses of clinical data calculated the threshold concentration of Paliperidone and the threshold doses of Risperidone. In addition to clinical data, *differential-activation* incorporates laboratory findings and biochemical variables such as 1) Risperidone metabolizes into a 22.65% lesser amount of Paliperidone, and 2) Neural responses to Paliperidone require a serum concentration that is three times higher (a 3/1 ratio) than the Risperidone response-threshold.

The calculated Risperidone serum concentration clinical efficacy threshold is 6.5 µg/L (see [Table 1](#) below). This is 27.2% of the Paliperidone efficacy-threshold. Thus, *differential-activation* occurs when a Risperidone serum concentration is below 27.2% of the Paliperidone threshold. Dose amounts for *differential-activation* vary according to body weight and severity of symptoms, and the severity of Bipolar symptoms fluctuates over time. Body weight is a useful constant factor in calculating dose-amounts and it can be useful for preliminary calculations of five-times-per-day low doses. Computations for dosages per body weights [14, 15, 16, 17] and serum concentrations are provided in [Table 1](#) and [Table 2](#).

## Results

### Guidelines for titration of adjunctive Valproic acid and low dose Risperidone

Adjunctive therapy with Valproic acid and Risperidone is more effective than Valproic acid monotherapy or Risperidone monotherapy. Each of these medications has a set of unique benefits that are therapeutically enhanced by the unique benefits of the other medication. One of the combined benefits is that Valproic acid increases digestive absorption of Risperidone into the blood stream, whereby lower doses of Risperidone achieve therapeutic plasma concentrations with Valproic acid adjunctive therapy. Conversely, Risperidone does not affect the plasma concentration of Valproic acid [3]. Starting therapy with just Valproic acid allows it to be titrated to its optimal efficacy without confusing its effects with effects of concurrent Risperidone titration. This eliminates the risk of cross-reaction overmedication during Valproic acid titration.

### Titration of Valproic acid ER

- a) The therapeutic blood-level of Valproic acid for Bipolar treatment is typically 85 to 125 mcg/mL [20].
- b) Exceeding 100 mcg/mL usually does not add significant benefits and there is a greater risk of side effects.
- c) Titration for Valproic acid ER: Add increments of 250 mg every two or three weeks until the patient is taking 500 mg at bedtime and 500 mg 12 hours later. Monitor for grogginess during titration.
- d) If there is no grogginess (or when it no longer occurs for a week), add the next titration dose.
- e) Some Bipolar patients can adequately manage their symptoms with Valproic acid monotherapy. Be vigilant for that possibility.
- f) Some Bipolar patients receive temporarily adequate symptom control from taking just Valproic acid during titration and for an individual-patient-dependent period of time following full titration, one to three months for some patients.
- g) If Valproic acid provides the patient with adequate symptom relief, do not add Risperidone unless/until Valproic acid adequate symptom relief wanes.
- h) Some Bipolar patients benefit from immediate adjunctive therapy with both Valproic acid and Risperidone in order to bring a quick halt to self harm or physical aggression.
- i) If it is appropriate, add Risperidone to fully titrated Valproic acid ER.

The Risperidone titration guidelines below were developed for the treatment method in this paper.

### Titration of Risperidone

#### Dose amounts

- a) Start with one 0.25 mg dose at bedtime to prevent initial grogginess during awake-hours. This should improve the quality of the patient's sleep without causing grogginess upon waking. If the patient

experiences grogginess upon waking, continue 0.25 mg only at bedtime until the grogginess stops. It usually stops within about five days.

b) If there is no grogginess (or when it no longer occurs) from dose-1, suggest adding a second 0.25 mg daily dose to be taken routinely at a time when the patient most often feels stressed. This should reduce the patient's stress and help prevent grogginess.

c) If there is no grogginess (or when it no longer occurs) from dose-2, suggest adding a third 0.25 mg daily dose to be taken routinely at a time when the patient most often feels stressed. This should reduce the patient's stress and help prevent grogginess.

d) If there is no grogginess (or when it no longer occurs) from dose-3, suggest adding a fourth 0.25 mg daily dose to be taken routinely at 3.8 to 4 hours before or after one of the current doses.

e) If there is no grogginess (or when it no longer occurs) from dose-4, suggest adding a fifth dose and set all doses at 3.8 to 4 hour intervals.

f) If the patient says it might be beneficial, increase one dose at a time until all doses are 0.5 mg, usually the optimal amount.

g) If you think an increase to a 0.5 mg routine would be helpful but the patient says No, invite him/her to try 0.5 mg at times of stress and let you how it feels.

h) Keep the patient supplied with a week or two of extra 0.25 mg tabs (35-70 pills) for temporary usage as-needed for controlling symptom exacerbations.

i) A routine regimen of one 0.5 mg tab every 3.8 hours (x5 per day) keeps most Bipolar-patients' nerves calm enough to noticeably reduce the frequency of significant exacerbations. When a "wave" hits a patient, taking an extra 0.25 mg tab with every other routine dose can control it. Taking an extra 0.25 mg tab with every routine dose can control a harsher "big wave". While a wave diminishes, a patient can avoid overmedication by decreasing the frequency of taking extra doses. When a wave is gone, a patient returns to the routine regimen. Patients who learn how and know they can control their waves become calmer and more reasonable in general. This leads to more secure self-esteem and better relationships with others.

j) It is valuable for a patient to set cell phone reminder-alarms to ring every 3.8 hours at medication-time.

k) It is valuable for a patient to not turn off the alarm sound until the scheduled pill is taken.

### Frequencies

Figure-3 below is a dose-administration timeline for steady efficacy using low amounts of Risperidone. After ingestion there is process of stomach digestion, bloodstream distribution, initial synaptic absorption, and increasing absorption. It typically takes 15-20 minutes for the synapses to absorb a

threshold amount that triggers significant responses. This results in a 15-20 minute onset time for noticeable effects. The amount of Risperidone in the bloodstream increases for 1 hour then gradually diminishes to below the synaptic threshold at about 4 hours. Efficacy ends and another dose taken at 4-hours will have a 15-minute onset time. Patients will have an uncomfortable and often very troublesome 15-20 minutes of being unmedicated every 4 hours.

The roller coaster is unnecessary and can be foregone by taking a second dose 10 minutes before the first dose loses effect. The serum concentration of a dose (Dose-1) wanes as it nears the termination of its 4-hour duration. A next dose (Dose-2) brings more concentration in a slope of increase that adds a bit to the Dose-1 waning-amount at the time when the waning would otherwise drop to an amount below the efficacy-threshold. The waning amount simultaneously adds a bit to the increasing amount at a time when the increasing amount would otherwise not yet be at the efficacy-threshold amount. The two amounts cumulatively keep the serum concentration above the efficacy-threshold. Dose-2 increases on a slope at the same pace as the decrease-slope of Dose-1. They combine to sustain serum concentration threshold equilibrium during the transition from Dose-1 to Dose-2. This occurs when Dose-2 is taken 10 minutes before Dose-1 wanes below the threshold. The diminishing efficacy of one dose is offset by the increasing efficacy of the next dose. The patient remains stable. There is no efficacy roller coaster with low doses of Risperidone every 3.8-hours (see [Figure-13](#) below).

A Risperidone 1 mg dose that corresponds with .01-mg/kg to .02-mg/kg does not meet or exceed the Paliperidone-activation threshold. A 1 mg low dose does not activate Paliperidone. It does, however, induce beneficial Risperidone responses.

An added benefit of low-dose treatment is that routine maintenance doses can be augmented with small extra doses during symptom exacerbations. This is possible because low doses metabolize 22.65% less Paliperidone than their own volume and because Paliperidone activation requires three times more serum volume than Risperidone activation requires. With low dose Risperidone, Paliperidone cannot be activated by small extra doses.

The treatment-paradigm in this paper differs from other Bipolar regimens in that it relies on accurate biochemistry and also fits patient-oriented perspectives. The new paradigm precludes 1) overmedication, 2) Paliperidone-increases of Serotonin and Prolactin, 3) false claims of *active moiety*, and 4) thirty-years of inaccurate research based on false *active moiety*. This new paradigm encourages treatment and minimizes dropout rates by providing markedly superior benefits without overmedication.

This author has implemented the superior method in this paper successfully for 14 years at a private practice Mental Health clinic that he owns and operates as a sole-proprietor single-providership since 1997. Four current patients use the method in this paper. They gave written consent to include their pertinent treatment and case history information in this paper. This paper is not a Multiple-Case-Study but some pertinent patient-information is valuable. One of the patients is a male 58-year-old Medical Doctor in treatment with this author for 13 years since 2008. Another patient is a 22 year-old woman in treatment with this author for six years since 2015. Another patient is a 21 year-old woman in treatment with this

author for four years since 2017. The other patient is a male 45 year-old schoolteacher in treatment with this author for seven months since early-2021.

The superior benefits of the treatment method in this paper are evidenced by this author's clinical case-observations, patient self-reports, and patient household-member reports. Patient self-reports of efficacy were positive and consistent within each patient across time. Individual patient self-reports were consistent with reports by other patients across all patients. Household members said the same things as patients and members of other households. Reports by patients and household members were consistent with this author's clinical case-observations. The information from patients and household members is reliable evidence that the method in this paper overcame the above-mentioned treatment-dropout rates and family fears of treatment.

Across all patients, household members participated in treatment at home in the similar ways. Notably: a) They could sense when a patient forgot to take medications. b) They used supportive tones and words in pointing out that medications were missed and should be taken now. c) They quickly sensed exacerbations of Bipolar-symptoms. d) They used supportive tones and words to calm the patient during exacerbations. e) They sensed when an extra "booster" tab of low dose medication was the best thing for resolving an exacerbation. f) They encouraged patients to take medications on time and attend regularly scheduled Therapy sessions. g) They supportively got the patient to page the Therapist (or page on behalf of the patient) for an emergency session when exacerbated symptoms were too severe to handle at home. h) They brought the patient to the clinic when exacerbated symptoms were too severe for the patient to drive safely.

Patients reported reliable treatment information that validates the benefits of the treatment method in this paper. Some key points that validate the method are:

1. The longevity of patient-treatments,
  1. Seven months
  2. Four years
  3. Six years
  4. Thirteen years
2. All of the patients consistently adhere to their medications
  1. Two patients started treatment as frequently-self-harming severely dysfunctional teenagers
  2. One patient is a knowledgeable and successful MD who started treatment 13 years ago
3. The MD, the 45 year-old, and the 22 year-old previously had other medications. They reported the regimen in this paper is markedly superior
4. Patient and household member reports state appreciation for the following features:
  1. The low doses provided stability without overmedication

2. The 3.8-hour dose-frequency sustained stability during transitions between doses
3. The x5 per day dosage sustained stability through the day
4. Sustained stability through the day contributed to better quality sleep at night
5. Consistent medication administration made symptom exacerbations less frequent and less severe
6. Use of extra doses as-needed enabled patient-control of symptom exacerbations
7. Flexible patient-control is a patient-oriented approach that engendered patient self-confidence and trust toward professional care

All of the involved patients have histories of quitting two to six or more other treatments in the past All of the patients and household members reported to this author, "You are the only one who knows what he's doing with medications and you're the only one who has actually helped." That says about everything that can be said to validate the benefits and superiority of the new paradigm presented in this paper. This paper presents a method of treating Bipolar Disorders with standard Valproic acid plus low-dose Risperidone every 3.8 hours. The purpose of this method is to optimize patients' therapeutic benefits. A part of this optimization is prevention of overmedication. Another part is differential-activation of Risperidone that neutralizes counter-therapeutic Paliperidone. Bipolar Disorder treatment using adjunctive Valporic acid and differential-activation-Risperidone yields significantly superior results of safety and efficacy.

## Discussion

We can't change the past but we can make a better future for 46-million Bipolar sufferers and their communities worldwide. When a person with a Bipolar Disorder starts Risperidone and Valproic acid it is important to maintain patient-comfort by preventing initial overmedication and grogginess. This can be done easily by introducing low doses and slow titration. Medication-grogginess is a tiredness of the body and slow/muddy thinking that often brings flattened or irritable emotions. Bipolar patients sense the slow grogginess more acutely than most other people because they are accustomed to hyperactive nerves and racing thoughts. Bipolar illness runs in family bloodlines. Many Bipolar families have a staunch fear of overmedication and of "all of that mental health crap". The fear is not false or delusional. The words "zombied" and "zombified" describe a reality that besets Bipolar patients more often than other people due to the sedation-factor in Bipolar medications. Bipolar families fear bad/excessive medications because the reality of bad/excessive medications induces well-justified and appropriate fear in Bipolar families.

## Conclusions

When Bipolar-medication grogginess occurs, it is real and it is not the patient's fault. It usually leads to "poor adherence" and quitting treatment. "Poor adherence" happens by true necessity because a person should discontinue treatments that induce harm. Quitting therapy also happens by true necessity because providers who overmedicate people are inept and patients should leave rather than rely on them. Every incident of side effects reinforces a Bipolar-family's fears and they deride members who "get help." Fearful families are highly unlikely to encourage treatment for America's 2,840,000 people with untreated severe Bipolar Disorders. A study in Korea reported a rapid increase in treatment dropout rates from month-1 (10.9%) to month-3 (24.7%) and it was 50.2% at month-36 [21]. Treatment providers told the researchers that the main reasons for quitting treatment were patients' denial of need, lack of efficacy, and patients' poor understanding of treatment effects. The providers were correct about "lack of efficacy" but they wrongly blamed patients' "denial" and "poor understanding of treatment effects."

This paper showed that widely accepted treatments for Bipolar Disorders are actually harmful to patients. Harmful treatments certainly "lack efficacy". Patients who quit harmful treatments are actually showing "good understanding of *harmful* treatment effects." Their awareness that they are being harmed is awareness that treatment "lacks efficacy." Providers wrongly say patients deny that they need help but patients quit treatment because it does not help. They quit because the treatment harms them. Providers' innate natural ego-defenses cannot see that the providers' are doing harm, so the patients are blamed for having poor insight. The patient-oriented truth is that patients appropriately refuse to continue accepting harmful prescriptions. Providers believe the medications are helpful because that is what they are taught to believe. Because they sincerely believe the medications are helpful, they do not believe patients who say the medications are bad. Providers tell each other, and tell themselves, that these are Bipolar Disorder patients who are crazy so it doesn't matter what they say about the medications. Therefore the widely accepted methods of treatment continue to be used and continue an 82% to 87% rate of failure.

This paper presents a vastly superior treatment for Bipolar Disorders. This author's patients have used this method since 2008. None have quit the treatment or said they want to return to their previous treatments. These patients are benefiting from a treatment that is very different from all others. It is the most important and valuable advent in Mental Health. The history of Bipolar Disorder treatment is an abysmal 82-87% failure. This paper presents the first successful treatment for Bipolar Disorders.

The challenge of creating a successful method for treating Bipolar Disorders has been met and overcome.

## List Of Abbreviations

AA: Arachidonic Acid

FDA: Food and Drug Administration

hr: hour(s)

J&J: Johnson & Johnson

kg: kilogram(s)

lb: pound(s)

MD: Medical Doctor

mg: milligram(s)

min: minute(s)

P: Paliperidone

R: Risperidone

µg/L: micrograms per liter

## **Declarations**

### Ethics approval and consent to participate

Not applicable

### Consent for publication

Four of this author's Bipolar Disorder patients and two household members signed statements allowing this paper to

include and publish some of their treatment information. They were not study-participants. No experiments were

conducted.

### Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary

information files.

### Competing interests

The author declares he has no competing interests.

### Funding

This author does strictly independent research and this study was entirely self-funded by the author.

### Authors' contributions

RT was the sole contributing author of this manuscript.

### Acknowledgements

Not applicable.

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## Tables

Due to technical limitations, tables 1 and 2 are only available as a download in the Supplemental Files section.

## Figures

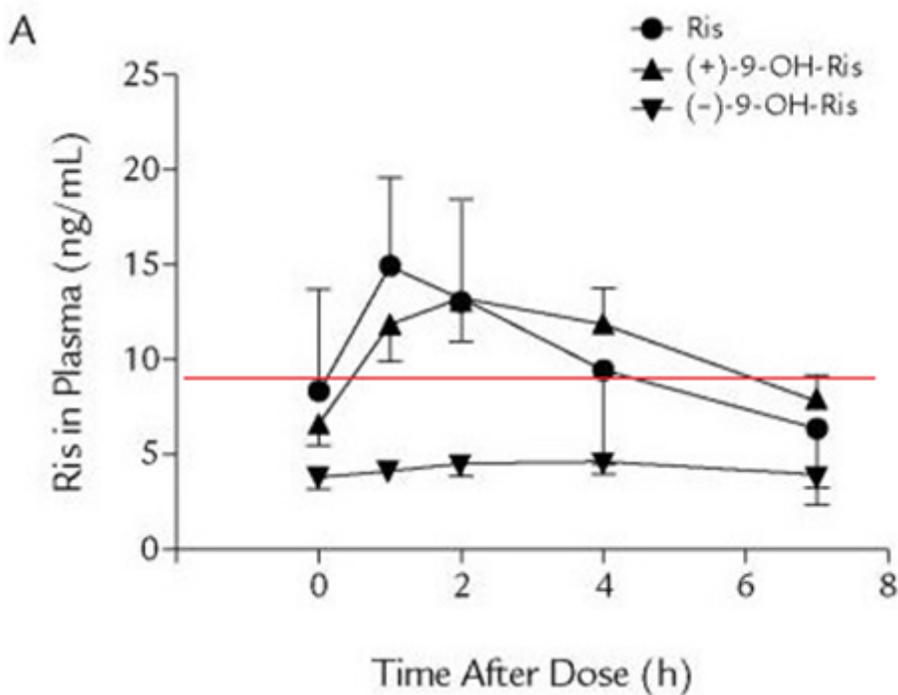


Figure 1

Graph A: Chemical-Risperidone and Paliperidone plasma durations Plasma concentration time profiles of chemical-Risperidone (Ris) and 9-hydroxyrisperidone enantiomers (+) and (-) 9-OH-Ris in 19 pediatric patients.

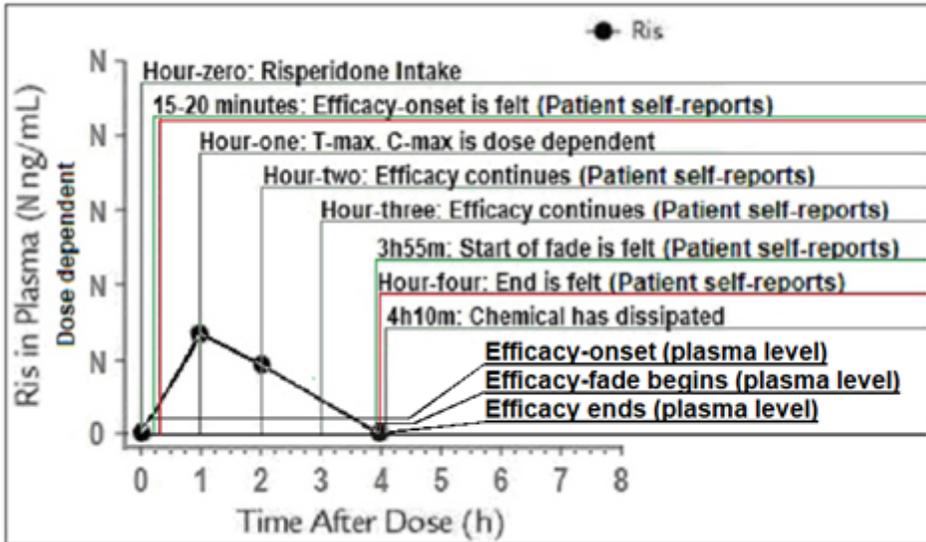


Figure 2

Graph B: Patient-reported efficacy onset and duration, and plasma concentration duration. Efficacy-onset at 15 to 20 minutes, efficacy-fade at 3-hours and 55-minutes, and efficacy-end at 4-hours were reported by this author's Bipolar Disorder patients and their household members and were observed by this author. The times of 1-hour T<sub>max</sub> and C<sub>max</sub>, and 4-hours/10-minutes chemical duration were reported by other research studies.

Signalling profile differences: paliperidone versus risperidone

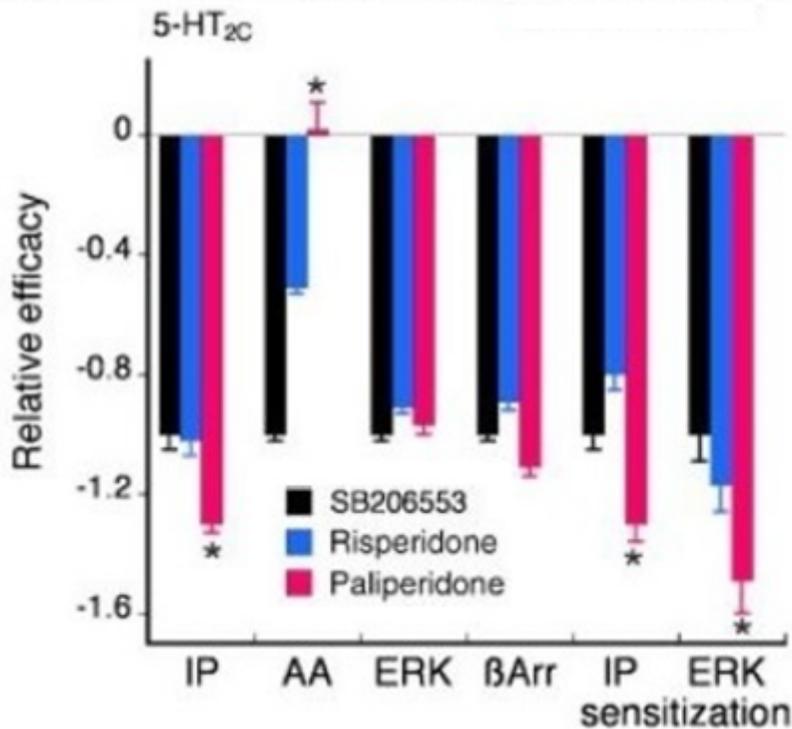


Figure 3

Graph C: Binding-affinity of Serotonin transporter-cells Risperidone (blue) significantly inhibited receptor sensitivity and absorption of Serotonin and significantly decreased the production and functions of Arachidonic Acid (AA) Serotonin transporter cells. Paliperidone (red) significantly increased receptor sensitivity and absorption of Serotonin and significantly increased Serotonin transport by AA cells.

**Signalling profile differences: paliperidone versus risperidone**

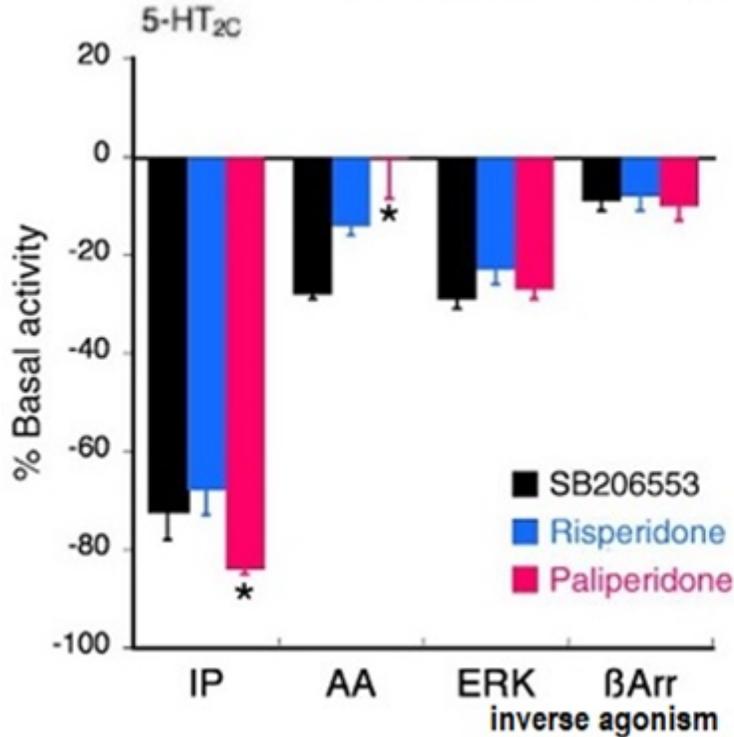
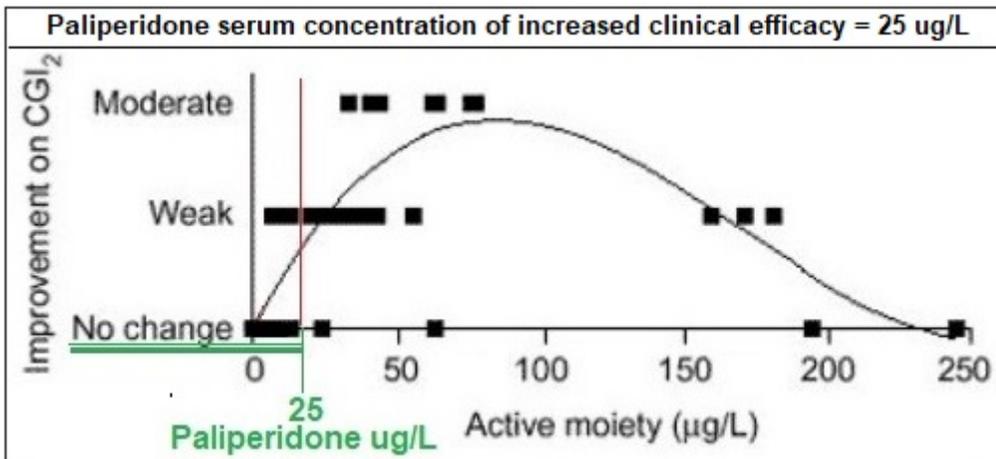


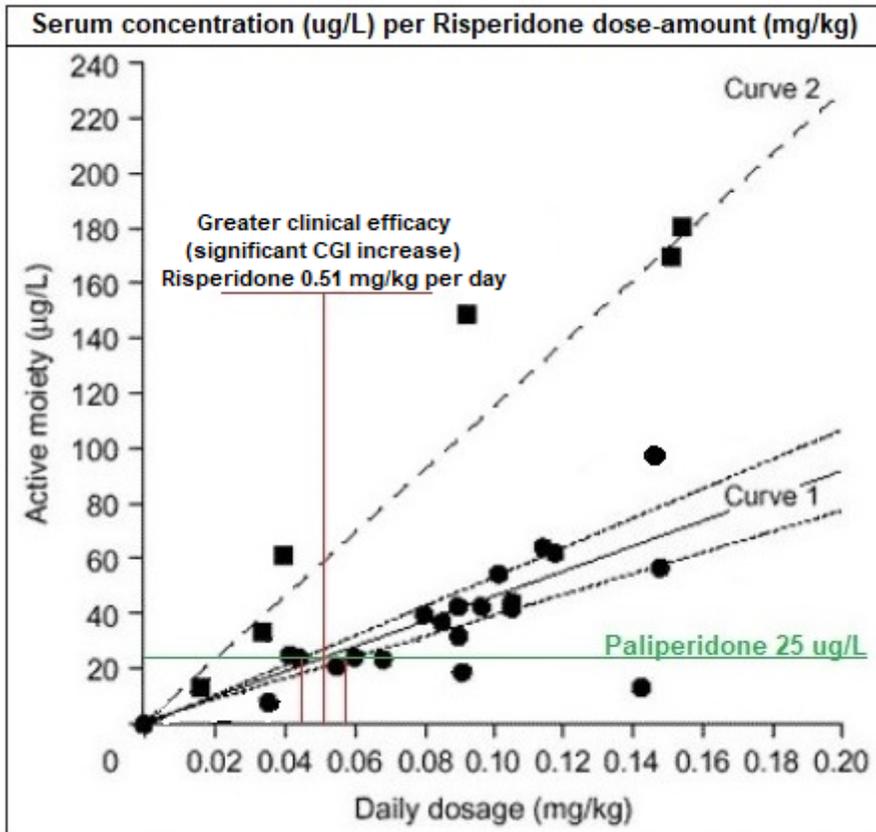
Figure 4

Graph D: Production/release of Serotonin transporter-cells The effects of maximal concentrations of Risperidone (1 μM) and Paliperidone (3 μM). At a concentration of 1 μM, Risperidone significantly reduced Arachidonic Acid (AA) basal activity. AA is a Serotonin transporter. At a higher concentration of 3 μM, Paliperidone did not significantly reduce AA basal activity.



**Figure 5**

Graph E: Paliperidone 25 ug/L triggers clinical efficacy This author overlaid red lines and green text showing that Paliperidone serum concentrations of  $\leq 25 \mu\text{g/L}$  were found in participants who demonstrated “no change” in CGI2 scores. Odou et al.10 defined “no change in CGI2 scores” as an absence of clinical improvement. This author overlaid a green line and green text showing the  $\leq 25 \mu\text{g/L}$  Paliperidone clinical-efficacy threshold from Graph E above. This author overlaid red lines and red text showing the dose-amount that corresponds with the  $\leq 25 \mu\text{g/L}$  threshold of clinical efficacy. (Graphs modified from Odou et al)[13].



**Figure 6**

Graph F: Daily amount of Risperidone for Paliperidone 25 ug/L This author overlaid red lines and green text showing that Paliperidone serum concentrations of  $\leq 25 \mu\text{g/L}$  were found in participants who demonstrated “no change” in CGI2 scores. Odou et al.10 defined “no change in CGI2 scores” as an absence of clinical improvement. This author overlaid a green line and green text showing the  $\leq 25 \mu\text{g/L}$  Paliperidone clinical-efficacy threshold from Graph E above. This author overlaid red lines and red text showing the dose-amount that corresponds with the  $\leq 25 \mu\text{g/L}$  threshold of clinical efficacy. (Graphs modified from Odou et al)[13].

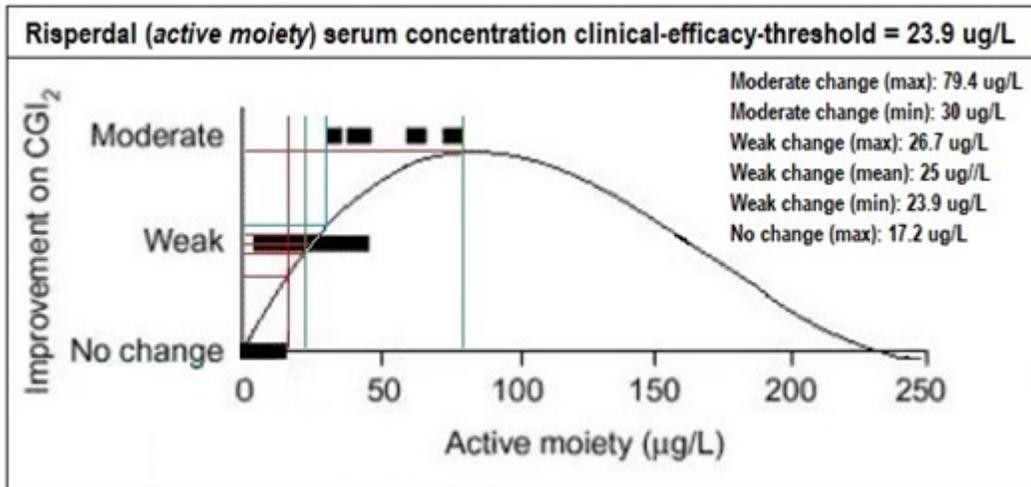
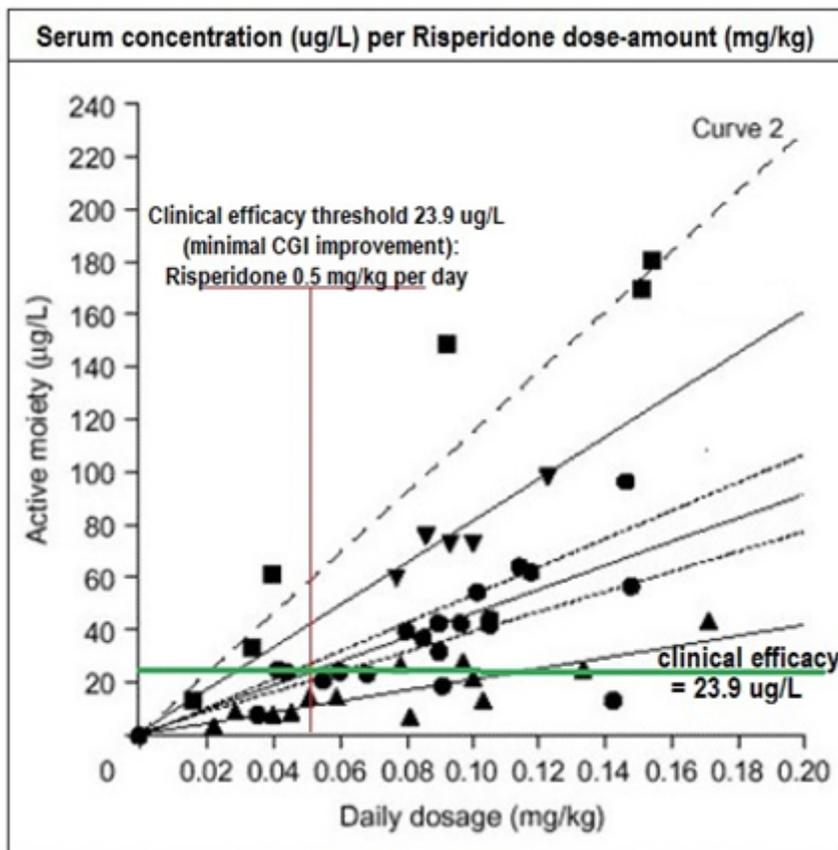


Figure 7

Graph G: Clinical Global Impression rating and plasma concentration The red, blue, and green lines in Graph G and the red and green lines in Graph H show y-axes/ x-axes intersections for pertinent ratio-criteria. Graph G depicts ratios of post-dose improvements (No change, Weak, Moderate) per active moiety serum concentrations ( $\mu\text{g/L}$ ). Y-axis improvements are measured by scores on the Clinical Global Impression (CGI) rating scale. The x-axis active moiety threshold-concentration for inducing improvement was  $23.9 \mu\text{g/L}$ . Graph H depicts ratios of active moiety serum concentrations ( $\mu\text{g/L}$ ) per total daily amounts of Risperidone ( $\text{mg/kg}$ ). The x-axis daily total threshold-amount for inducing active moiety clinical-efficacy was  $.05 \text{ mg/kg}$ . (Graph modified from Odou et al)[13].



## Figure 8

Graph H: Amount of Risperidone for Paliperidone 23.9 ug/L The red, blue, and green lines in Graph G and the red and green lines in Graph H show y-axes/ x-axes intersections for pertinent ratio-criteria. Graph G depicts ratios of post-dose improvements (No change, Weak, Moderate) per active moiety serum concentrations ( $\mu\text{g/L}$ ). Y-axis improvements are measured by scores on the Clinical Global Impression (CGI) rating scale. The x-axis active moiety threshold-concentration for inducing improvement was 23.9  $\mu\text{g/L}$ . Graph H depicts ratios of active moiety serum concentrations ( $\mu\text{g/L}$ ) per total daily amounts of Risperidone ( $\text{mg/kg}$ ). The x-axis daily total threshold-amount for inducing active moiety clinical-efficacy was .05  $\text{mg/kg}$ . (Graph modified from Odou et al)[13].

## How much does the average American man weigh?

The average American man 20 years old and up weighs **197.9 pounds**<sup>®</sup>. The average waist circumference is 40.2 inches, and the average height is just over 5 feet 9 inches (about 69.1 inches) tall.

When broken down by age group, the average weights for American men are as follows:

Age group (Years)	Average weight (Pounds)
20-39	196.9
40-59	200.9
60 and older	194.7

Your weight	197.9 <a href="#">lb</a> ▾
Dosage	0.05 <a href="#">mg</a> ▾ /kg
Frequency	<a href="#">once per day</a> ▾
Total daily dose	4.488 <a href="#">mg</a> ▾

**(a)**

## Figure 9

Average weight of USA adult males a: Paliperidone minimum-efficacy daily dose-amount of Risperidone for average-weight USA males

## How much does the average American woman weigh?

The average American woman 20 years old and up weighs **170.6 pounds** and stands at 63.7 inches (almost 5 feet, 4 inches) tall.

And the average waist circumference? It's 38.6 inches.

As of 2016, the **average weights for women in different age groups were**:

Age group (years)	Average weight (pounds)
20-39	167.6
40-59	176.4
60 and older	166.5

Your weight	170.6 <b>lb</b>
Dosage	0.05 <b>mg</b> /kg
Frequency	<b>once per day</b>
Total daily dose	3.869 <b>mg</b>

**(a)**

**Figure 10**

Average weight of USA adult females a: Paliperidone minimum-efficacy daily dose-amount of Risperidone for average-weight USA females

**Ideal Body Weight Charts  
For Men 25-59 years of age.**

Height in Feet&Inches	Small Frame	Medium Frame	Large Frame
5'2"	128-134	131-141	138-150
5'3"	130-136	133-143	140-153
5'4"	132-138	135-145	142-156
5'5"	134-140	137-148	144-160
5'6"	136-142	139-151	146-164
5'7"	138-145	142-154	149-168
5'8"	140-148	145-157	152-172
5'9"	142-151	151-163	155-176
5'10"	144-154	151-163	158-180
5'11"	146-157	154-166	161-184
6'0"	149-160	157-170	164-188
6'1"	152-164	160-174	168-192
6'2"	155-168	165-178	172-197
6'3"	158-172	167-182	176-202
6'4"	162-176	171-187	181-207

$(142+151+151+163+155+163) \div 6 = 156.66 \text{ pounds}$

Your weight	156.66 <a href="#">lb</a> ▾
Dosage	0.05 <a href="#">mg</a> ▾ /kg
Frequency	<a href="#">once per day</a> ▾
Total daily dose	3.553 <a href="#">mg</a> ▾

**(a)**

**Figure 11**

Mean weight of average-height USA males a: Paliperidone minimum-efficacy daily dose-amount of Risperidone for healthier-weight males

**Ideal Body Weight Charts  
For Women 25-59 years of age.**

Height in Feet&Inches	Small Frame	Medium Frame	Large Frame
4'10"	102-111	109-121	118-131
4'11"	103-113	111-123	120-134
5'0"	104-115	113-126	122-137
5'1"	106-118	115-129	125-140
5'2"	108-121	118-132	128-143
5'3"	111-124	121-135	131-147
5'4"	114-127	124-138	134-151
5'5"	117-130	127-141	137-155
5'6"	120-133	130-144	140-159
5'7"	123-136	133-147	143-163
5'8"	126-139	136-150	146-167
5'9"	129-142	139-153	149-170
5'10"	132-145	142-156	152-173
5'11"	135-148	145-159	155-176
6'0"	138-151	148-162	158-179

$(114+127+124+138+134+151) \div 6 = 131.33$  pounds

Your weight **131.33 lb**

Dosage **0.05 mg** /kg

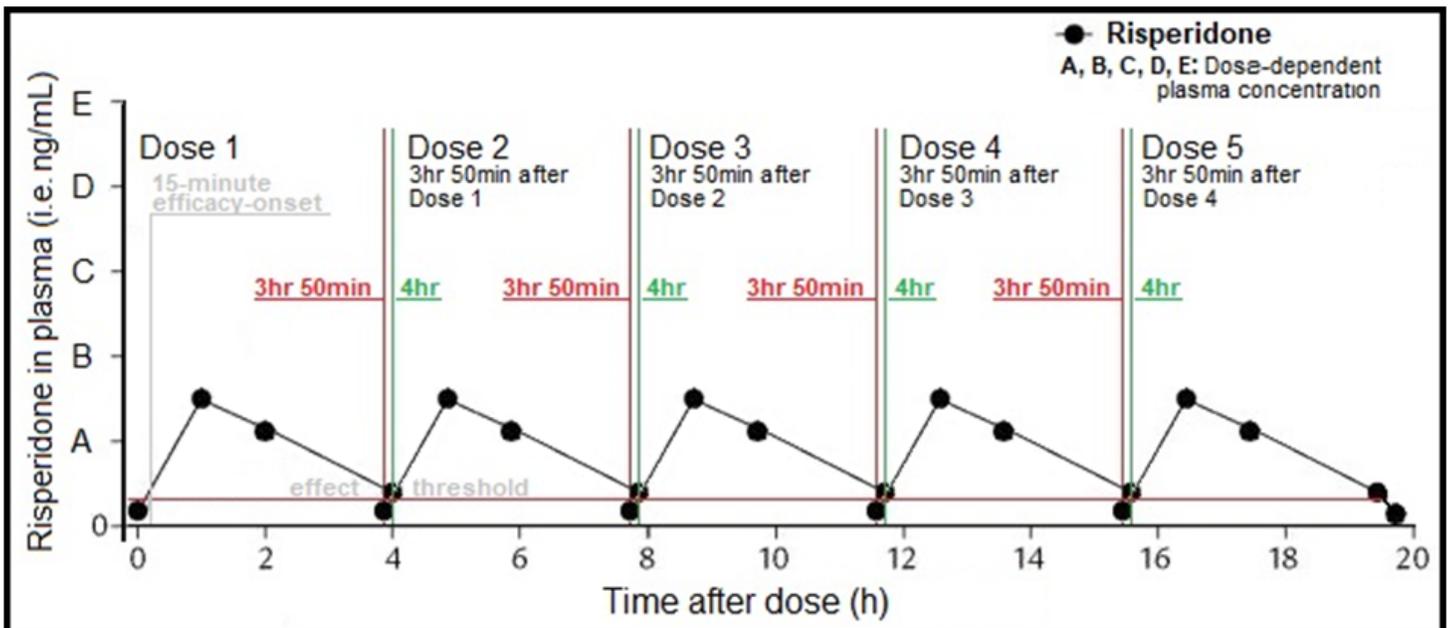
Frequency **once per day**

Total daily dose **2.9785 mg**

**(a)**

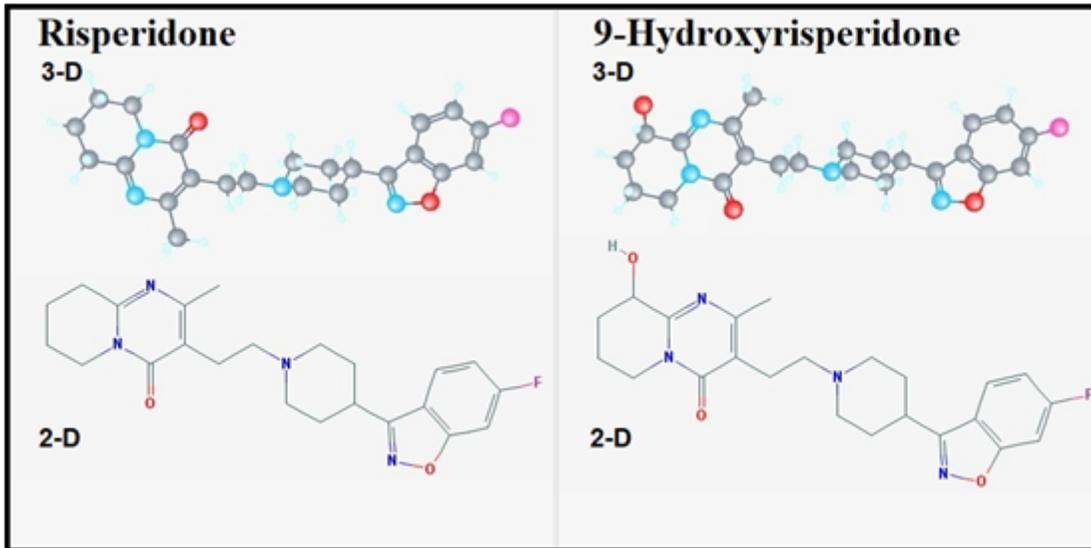
**Figure 12**

Mean weight of average-height USA females a: Paliperidone minimum-efficacy daily dose-amount of Risperidone for healthier-weight females



**Figure 13**

Risperidone 3.8-hour dosing Doses are taken at 3-hours/50-minutes, 10 minutes before the hour-4 efficacy-termination of a previous dose. A 15-to-20-minute dose-onset of increasing plasma concentration additively combines with the decreasing concentration of a terminating previous dose. The additive combining of concentrations sustains an efficacy-sufficient concentration across sequential doses.



**Figure 14**

Diagrams of chemical-Risperidone and 9-Hydroxyrisperidone 2-D and 3-D diagrams show a single molecule difference in chemical-Risperidone and 9-Hydroxyrisperidone.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalinformation.docx](#)
- [Tables.docx](#)