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Adjunctive 5-hydroxytryptophan slow-release for treatment-resistant depression: Clinical and pre-clinical rationale

Jacob P.R. Jacobsen, PhD[1], **Andrew D. Krystal, MD**[2], **K. Ranga R. Krishnan, MD**[3], and **Marc G. Caron, PhD.**[1,4,5]

[1]Department of Cell Biology, Duke University, Durham, NC 27710, USA

[2]Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC 27710, USA

[3]Rush Medical College, Chicago, IL 60612, USA

[4]Department of Medicine, Duke University, Durham, NC 27710, USA

[5]Department of Neurobiology, Duke University Medical Center, Durham, NC 27710, USA

Abstract

Serotonin transporter (SERT) inhibitors treat depression by elevating brain extracellular 5-hydroxytryptamine (5-HT_{Ext}). However, only one-third of patients respond adequately. Treatment-resistant depression (TRD) is a major unmet need. Interestingly, elevating 5-HT_{Ext} beyond what is achieved by a SERT inhibitor appears to treat TRD. Adjunctive administration of 5-hydroxytryptophan (5-HTP) safely elevates 5-HT_{Ext} beyond the SERT inhibitor effect in humans; but, 5-HTP cannot be a clinically viable drug because of its poor pharmacokinetics. A slow-release (SR) delivery mode would be predicted to overcome the pharmacokinetic limitations of 5-HTP, substantially enhance the pharmacological action, and transform 5-HTP into a clinically viable drug. Animal studies bear out this prediction. Thus, adjunct 5-HTP SR could be an important new treatment for TRD. Here we review the clinical and preclinical evidence.

Keywords

Antidepressant; depression; treatment-resistant depression; 5-hydroxytryptophan

Current therapies for treatment-resistant depression are inadequate

Depression is characterized by persistent depressed mood and/or anhedonia in conjunction with other mood and physical symptoms (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition). According to statistics from the USA National Institute of Mental Health, 6.6 % of the population will suffer from depression each year. The mainstay of antidepressant therapy remains the serotonin transporter (SERT) inhibitors, predominantly

Corresponding author: Marc G. Caron, Room 0487 CARL Building, Box 3287, Duke University Medical Center, Durham, NC27710. +1 919 684 5433 (tel). +1 919 681 8641(fax). marc.caron@dm.duke.edu.

Conflicts of Interest

JPRJ and MGC are inventors on US patents pertaining to the adjunct 5-HTP SR method-of-treatment, and hold stock in Evecxia Inc., a company founded to develop a 5-HTP SR drug. ADK and RRK serve on the Evecxia Scientific Advisory Board.

selective serotonin reuptake-inhibitors (SSRIs) and dual *serotonin and norepinephrine reuptake inhibitors* (SNRIs). SERT inhibitors block reuptake of 5-HT from the extracellular space. This causes sustained elevation of brain extracellular serotonin (*aka* 5-hydroxytryptamine, 5-HT_{Ext}), which over time leads to an antidepressant response [1]. Unfortunately, SERT inhibitors achieve remission in only a third of patients [2]. As such, an estimated 2 % of the population suffers from treatment-resistant depression (TRD) [3]. Current treatments for TRD are of limited benefit [4], and new treatments are needed.

As reviewed below, multipronged clinical data suggest that elevating 5-HT_{Ext} beyond the effect achieved by SERT inhibitor monotherapy is therapeutic in TRD. Hence, a drug that, when administered adjunct to a SERT inhibitor, safely and in a sustained fashion, elevates 5-HT_{Ext} beyond the SSRI effect could be a new therapy for TRD. The aim of this article is two-fold: (**i**) To review the evidence that elevating 5-HT_{Ext} beyond the SERT inhibitor effect treat TRD. (**ii**) To present the hypothesis that adjunct treatment with a slow-release (SR) formulation of the 5-HT precursor *5-hydroxytryptophan* (5-HTP; Figure 1) will be a safe and effective way to elevate 5-HT_{Ext} beyond the SERT inhibitor effect. Further, we highlight three critical points regarding 5-HTP pharmacology, not clearly recognized or articulated previously: (**i**) 5-HTP by itself only modestly elevates 5-HT_{Ext}, whereas adjunctive 5-HTP strongly and synergistically augments SERT inhibitor-induced 5-HT_{Ext} elevation. (**ii**) Combining 5-HTP with a SERT inhibitor appears quite safe in humans. (**iii**) Poor pharmacokinetics, i.e. rapid absorption and elimination, prohibit 5-HTP from being a clinically viable drug in its native, immediate release (IR), form. Importantly, convergent data suggest a SR delivery mode will remedy 5-HTP's pharmacokinetic limitations and produce a drug with general therapeutic potential in TRD.

The need for sustained 5-HT_{Ext} elevation in depression therapy

5-HT_{Ext} elevation remains the best validated antidepressant mechanism [1]. Further, the evidence indicates that the 5-HT_{Ext} elevation must be sustained to achieve a clinically viable antidepressant effect.

Risk of relapse

A critical observation supporting the necessity of sustained elevation of 5-HT_{Ext} is that acutely lowering brain 5-HT_{Ext} by eliminating dietary tryptophan, a precursor of 5-HT, precipitates a return of depression symptoms in 50 % of patients otherwise remitted on a SERT inhibitor. The relapse occurs within hours [5–7]. In rat models of tryptophan depletion – where the procedure lowers plasma tryptophan as in humans (by 80 %) - brain 5-HT_{Ext} rapidly drops by 50 %, from the initial, SERT inhibitor-elevated level [8]. Thus, it appears an acute 50 % drop in brain 5-HT_{Ext} will trigger acute relapse in 50 % of depression patients otherwise treated to remission with a SERT inhibitor.

Risk of discontinuation syndrome

An additional consideration is that lapse of sustained elevation in 5-HT_{Ext} can precipitate specific adverse events. Specifically, missing even a single dose of a SERT inhibitor can occasionally precipitate *discontinuation syndrome* [9], characterized by dizziness, nausea,

lethargy and headache. In animals, SSRI-induced 5-HT_{Ext} elevation rapidly reverts to baseline upon SSRI-withdrawal [10]. For the short-acting SNRI *venlafaxine* ($T_{1/2}$ = 8h [average for parent compound and active metabolite]), the discontinuation syndrome is more frequent, and can occur within hours [11]. Because of the short $T_{1/2}$, venlafaxine is used predominantly in its SR version. In a head-to-head antidepressant trial, venlafaxine SR was superior to venlafaxine IR [12]. All marketed SSRIs have $T_{1/2}$ > 20h. This leads to < 0.3 fold steady-state drug level fluctuations, hence minimal fluctuations in SERT occupancy, and hence essentially stable 5-HT_{Ext}, so that discontinuation do not occur with once-daily dosing [13] (Figure 2).

Thus, for antidepressant therapy, 5-HT_{Ext} elevation must be sustained and cannot drop off, lest risk of relapse and discontinuation syndrome.

Elevating 5-HT_{Ext} beyond the SERT inhibitor effect has shown promise in treating TRD

Brain 5-HT_{Ext} levels are regulated on multiple levels

The SERT is one of several elements controlling 5-HT_{Ext} [14]. 5-HT synthesis [15], -degradation [16], -neuronal firing [17], -conjugations [18], and feed-back mechanisms [19] are all important determiners of 5-HT_{Ext} levels. For instance, in the rat brain, levels of glucuronide-conjugated 5-HT_{Ext}, which does not bind to 5-HT receptors, is twice that of free 5-HT_{Ext} [18]. In a naturalistic mouse model of brain 5-HT deficiency - due to a reduction-of-function mutation in tryptophan hydroxylase 2, the rate-limiting enzyme in brain 5-HT synthesis - chronic SSRI treatment only modestly elevated 5-HT_{Ext} [15, 20]. This implies that 5-HT reuptake is a less important determiner for 5-HT_{Ext} under 5-HT deficiency, a putative risk factor in depression [21]. From 5-HT neurobiology, it appears logical that selective SERT inhibition will not in all patients realize the full antidepressant potential of elevating 5-HT_{Ext}. Indeed, substantial preliminary clinical evidence suggests that elevating 5-HT_{Ext} beyond the SSRI inhibitor monotherapy effect has efficacy in TRD, or accelerates antidepressant onset [22–37]. Below we review key examples.

Adjunctive drugs elevating 5-HT_{Ext} beyond the effect of SERT inhibition augment the antidepressant effect

Adjunctive *pindolol* elevates 5-HT_{Ext} beyond the SSRI effect for a limited period early during SSRI treatment, by preferentially blocking inhibitory 5-HT_{1A} auto-receptors [38, 39]. In double-blind trials, adjunctive pindolol accelerates the antidepressant onset [40, 41]. In contrast, pindolol augmentation has limited efficacy in TRD [24], consistent with that chronic SSRI treatment already inactivates 5-HT_{1A} auto-receptors over time. Further, pindolol is disadvantaged by a short $T_{1/2}$ of 4h [42] and a narrow therapeutic window [43]. Adjunctive treatment with the monoamine oxidase inhibitor (MAO I) *moclobemide* elevates 5-HT_{Ext} beyond the SSRI effect by inhibiting 5-HT degradation [44]. In open trials, adjunctive moclobemide is reported to treat TRD to SSRIs [26–28]. However, this strategy has the limitation that SSRI + moclobemide co-treatment occasionally triggers serious adverse events [29, 30]. In double-blind trials, adjunctive treatment with the 5-HT precursor *tryptophan* augments the efficacy of SERT inhibitors [31, 32]. However, this approach has

the limitations that just a few percent of tryptophan is metabolized to 5-HT [45], and that tryptophan's short $T_{1/2}$ of 3h [46] necessitates frequent dosing. Likewise, as detailed below, adjunctive treatment with the immediate 5-HT precursor *5-HTP* is reported to confer efficacy in TRD to SERT inhibitors. Recently, in double-blind trials, adjunctive treatment with *methylfolate* was reported to be effective in TRD patients who had failed SSRIs [33]. Methylfolate enhances the biosynthesis of tetrahydrobiopterin, a co-factor in 5-HT, DA, and NA synthesis [47]. It should be noted that adjunctive drugs that selectively elevate NA_{Ext} or DA_{Ext} fail to show efficacy in TRD [48, 49]. Therefore, methylfolate presumably acts by increasing brain 5-HT levels available for release by SSRI treatment, i.e. by elevating 5-HT_{Ext} beyond the SSRI effect. However, the extent to which methylfolate increases brain 5-HT levels is unknown. Altogether, clinical evidence, from use of five different adjunctive compounds, converges in suggesting that TRD can be treated by elevating 5-HT_{Ext} beyond the levels achieved by a SERT inhibitor.

Indirect pre-clinical evidence

Several presumably non-serotoninergic adjunctive drugs with varying degrees of evidence for efficacy in TRD in humans elevate 5-HT_{Ext} to varying degrees beyond the SERT inhibitor effect in rodents. These include adjunctive *lithium* [50], *modafinil* [51], and *atypical antipsychotics* [52, 53]. Thus, it is reasonable to hypothesize that 5-HT_{Ext} elevation plays a role in the therapeutic action in TRD of some adjunctive drugs that do not have direct 5-HT_{Ext} elevating effects.

Acute adjunctive 5-HTP elevates 5-HT_{Ext} beyond the SERT inhibitor effect

In rodents, at moderate parenteral doses (10–40 mg/kg), 5-HTP alone only modestly elevates 5-HT_{Ext}. In contrast, adjunctive 5-HTP strongly and synergistically elevates 5-HT_{Ext} beyond the SSRI effect [54, 55]. In one acute study in rats, 20 mg/kg 5-HTP or an SSRI elevated 5-HT_{Ext} by 100 % and 250 %, respectively, whereas 5-HTP plus the SSRI elevated 5-HT_{Ext} by 850 % [55]. The same synergism in rats was observed using an acute rise in plasma corticosteroids as a peripheral biomarker of an acute elevation in brain 5-HT_{Ext} [56]. Similarly, in human healthy volunteers, Lowe *et al.* found that oral 200 mg 5-HTP or an SSRI elevated cortisol by 35 % and 100 %, respectively. However, 5-HTP combined with the SSRI elevated cortisol by 500 % [57]. Notably, acute 5-HTP + SSRI, and to a lesser extent acute SSRI alone, caused rapid onset vomiting and nausea in some subjects [57], indicating that sudden surges in bodily 5-HT levels are not well tolerated. In depression or OCD patients, Meltzer *et al.* also administered acute oral 200 mg 5-HTP and measured the cortisol rise, either before or during chronic SSRI treatment. The cortisol rise after acute administration of 5-HTP was two-fold larger during SSRI treatment than prior to it [58]. No adverse events were observed in this study, conceivably because chronic SSRI administration adapts the gastrointestinal tract to increased 5-HT stimulation. Likewise, in depression patients Sargent *et al.* administered acute oral 100 mg 5-HTP and measured the cortisol rise, before and during chronic treatment with an SSRI. The cortisol rise after acute 100 mg 5-HTP was four-fold larger during SSRI treatment than prior it. Again, no adverse events were observed [59].

Combined, the published pre-clinical and clinical data suggest the following: (**i**) 5-HTP elevates 5-HT_{Ext} more potently when adjunct to a SERT inhibitor than when administered by its own. (**ii**) Adjunctive 5-HTP can elevate 5-HT_{Ext} beyond the SERT inhibitor effect safely.

5-HTP has shown promising antidepressant effects, but poor pharmacokinetics limits the therapeutic potential

The pharmacokinetics of 5-HTP

Native 5-HTP IR is a poor serotonergic antidepressant. As discussed above, effective antidepressant therapy requires sustained, minimally fluctuating 5-HT_{Ext} elevation [5, 9]. A $T_{1/2}$ = 2h means that even at thrice-daily dosing 5-HTP plasma levels will fluctuate at least 5-fold at steady-state. This contrasts to the less than 0.3-fold steady-state plasma fluctuations of most SSRIs [13] (Figure 2). Further, 5-HTP's fast-onset adverse events likely results from the rapid absorption and resultant 5-HT spikes upon administration. Co-administering a *peripheral amino acid decarboxylase inhibitor* (DCI) with 5-HTP will modestly extend the $T_{1/2}$, several-fold enhance exposure, and not affect T_{Max} [60]. Including a DCI in a 5-HTP SR drug could be beneficial, but could complicate formulation development, dosing, and safety.

5-HTP as an antidepressant

5-HTP has never been formally developed as a drug and optimized dosage forms and dosing regimens are unavailable. Further, all previous 5-HTP trials were small, including at most a few dozen subjects. In contrast, to ensure reasonable statistical power, a typical antidepressant proof-of-concept Phase II trial includes 50–100 subjects per arm [61]. Most trials used 5-HTP monotherapy; but, as noted above, 5-HTP may be more relevant as an adjunctive, augmentation therapy. For these reasons in aggregate, previous trials may inherently have underestimated the antidepressant potential of 5-HTP. Nevertheless, most 5-HTP antidepressant reports are positive [45]. Scholarly reviews conclude 5-HTP has shown promise as an antidepressant, and that more and better trials are warranted [45, 62]. Consistent with its pharmacology, 5-HTP antidepressant effect appears to be more consistent when adjunctive to another 5-HT_{Ext}-elevating antidepressant [45]. In the following we briefly review such adjunctive 5-HTP trials published in English (and see Table 1).

In a double-blind trial in depressed inpatients, Alino *et al.* [34] found that nialamide (MAO inhibitor) + 5-HTP (200 mg/day) was superior to nialamide alone. The worst reported adverse events were diarrhea. In an open-label case-series of 99 chronic TRD patients, most already on SERT inhibitor therapy, van Hiele [35] found that 5-HTP (average dose 200 mg/day) + DCI treatment induced a "remarkable recovery" in ~50 % of patients. Antidepressant responses tended to be all-or-none. Few adverse events were reported, mostly nausea. Hypomania occurred in 15 patients, which reversed upon lowering the 5-HTP dose. In a four-arm double-blind placebo-controlled trial in depressed inpatients, van Praag *et al.* [36] compared placebo with clomipramine (a SERT inhibitor), 5-HTP (200 mg/day) + DCI, and clomipramine + 5-HTP + DCI. Clomipramine + 5-HTP + DCI was superior to all other arms. Nausea was the most common adverse events. In a double-blind trial in depressed

inpatients, Nardini *et al.* [37] found that clomipramine + 5-HTP (300 mg/day) was superior to clomipramine alone. Adverse events were reported to be few.

These pilot data on efficacy and safety of adjunct 5-HTP in TRD are encouraging. Similar pilot trials provided initial evidence of antidepressant efficacy of tricyclic antidepressants and ketamine [63, 64]. The data add to the larger rationale supporting adjunctive 5-HTP SR as a novel therapy for patients who respond inadequately to SERT inhibitors (Figure 3).

5-HTP has a good oral human safety record

Experience from >100 published clinical trials and widespread nutraceutical use suggests that oral 5-HTP - in high milligram to low gram doses, alone or as an adjunct to other serotonergic drugs, with or without a DCI - has a low propensity to cause severe adverse events in humans [45, 65, 66].

5-HTP has not been reported to cause serotonin syndrome in humans

Serotonin syndrome is a toxic state caused by excessive 5-$HT_{Ext.}$ Severe serotonin syndrome is rare, and almost exclusively caused by SERT inhibitor + MAO inhibitor co-treatment [67]. 5-HTP has never been associated with serotonin syndrome in humans. In published reports, > 250 humans have been dosed with 5-HTP + a SERT inhibitor, with no serious adverse events [35–37, 57–59, 68–70]. A MAO inhibitor blocks the metabolic flow through the 5-HT pathway, at the point of degradation, which might lead to extreme build-up of 5-HT_{Ext}. In contrast, 5-HTP increases 5-HT synthesis and the dynamic flow through the 5-HT pathway, which might not easily lead to 5-HT_{Ext} build-up.

In rodents, high parenteral acute bolus doses of 5-HTP, e.g. 100 mg/kg, in combination with an SSRI can cause transient serotonin syndrome [71]. However, this is an artefact of preclinical pharmacology methodology, i.e. extreme doses and non-oral routes of administration. Similar high parenteral doses of *fluoxetine*, *methylphenidate*, and *caffeine* often kill rodents [72], whereas in humans these compounds are extremely safe, in their appropriate oral doses and dosage forms.

Common 5-HTP adverse events are gastrointestinal

In humans, acute and long term treatment with 5-HTP, even at high doses, has minimal effects on cardiovascular, hepatic, renal, hematological, or urinalysis parameters (reviewed in [65, 73]). Similar, in rats, a 1-year toxicology study found no effects of oral high-dose 5-HTP (875 mg/kg/day, via the drinking water) on cardiovascular, hepatic, renal, hematological, body weight gain, organ histology, and organ weight parameters [74]. In humans, common adverse events seen with oral 5-HTP are mild to moderate, and gastrointestinal, e.g. nausea or stomach cramps, and less frequently diarrhea and vomiting (reviewed in [73]). Occasional adverse events include hypomania, headaches, lightheadedness, and palpitations. Often onset is rapid, which is likely due to rapid conversion of 5-HTP to 5-HT upon dosing with standard 5-HTP IR [35, 45, 57]. Interestingly, two studies report that using enteric coated 5-HTP capsules, which delays 5-HTP delivery until the intestine, substantially reduces gastrointestinal adverse events [35, 36]. This suggests a direct irritating effect of 5-HTP on the stomach. Most studies do not

specify if they administered 5-HTP with enteric coating. On the other hand, vomiting and nausea could be centrally, rather than peripherally, mediated. Evidence for this is that upon acute bolus 5-HTP administration, DCI co-treatment (which reduces peripheral and increases central 5-HTP conversion to 5-HT) can induce nausea and vomiting at 5-HTP doses (100–200 mg) otherwise devoid of adverse events [60, 75, 76]. Further, acute co-treatment of 5-HTP IR 200 mg + SSRI causes vomiting and nausea [57], but acute 5-HTP IR 200 mg causes no adverse events when added after 4 weeks prior SSRI treatment [58]. In any case, 5-HTP gastrointestinal adverse events lessen or disappear over time [73], as occurs with SSRIs [77]. Overall, the evidence suggests that gastrointestinal adverse events after adjunctive 5-HTP can be greatly reduced if (**i**) the 5-HTP C_{max} in plasma is minimized, (**ii**) appropriate 5-HTP formulations are used, and (**iii**) SSRI treatment has lasted several weeks prior to the start of 5-HTP dosing.

Slow-release delivery will transform the therapeutic potential of 5-HTP

A SR formulation delivers an active pharmaceutical ingredient (API) over many hours, thereby delaying the time (T_{Max}) to peak plasma levels (C_{Max}) and increasing the $T_{1/2}$. An SR formulation is particularly beneficial when (**i**) $T_{1/2}$ is very short, (**ii**) sustained API exposure is required, (**iii**) adverse events are linked to early high peak API levels, and (**iv**) less frequent dosing than necessary with the IR formulation is required. All points apply to 5-HTP. As parallels, some drugs with fast pharmacokinetics similar to 5-HTP's are only safe and effective in their SR versions [78, 79]. The PK of 5-HTP IR - rapid absorption, short duration of action – is the opposite of that required by a serotonergic antidepressant, where constant and minimally fluctuating drug exposure is mandated [5–7, 9]. Unless taken very frequently, 5-HTP in its native IR form will not produce sustained exposure [60]. At the same time, adherence to more than once or twice daily dosing is unrealistic for antidepressants, which are taken for months or years, and mostly by outpatients [80–82]. A SR formulation would produce lower 5-HTP plasma C_{max}, provide the necessary sustained 5-HTP exposure, allow for higher doses, and bring the dosing frequency to requisite once or twice daily. Thus, in theory a SR formulation would uniquely improve the therapeutic potential of 5-HTP as an antidepressant in an everyday clinical setting (Figure 4).

In mouse models, 5-HTP SR transforms the therapeutic potential of 5-HTP

Directed by the clinical data reviewed above we carried out an adjunctive 5-HTP SR proof-of-concept study in mice [83]. We modeled 5-HTP SR using subcutaneous minipumps, which produces constant (zero-order) SR delivery. Adjunctive 5-HTP SR augmented the 5-HT_{Ext}-elevation induced by chronic SSRI, by 100 % in wildtype mice and by 800 % in mice with naturalistic 5-HT deficiency [15, 20], respectively. We observed no adverse events. Had minipump capacity not limited the 5-HTP SR dose to 100 mg/kg/day, even stronger 5-HT_{Ext}-augmentation could have been achieved. As expected, 5-HTP SR alone had only modest effects on 5-HT_{Ext}. When modeling adjunctive 5-HTP IR by administering 2 × 50 mg/kg (AM and PM) daily subcutaneous bolus 5-HTP injections, we observed large, transient spikes in 5-HT_{Ext}, accompanied by marked gastrointestinal adverse events and mild seizures. Low-dose adjunct 5-HTP IR, 2 × 3.125 mg/kg barely augmenting 5-HT_{Ext}, but still caused adverse events - even while the peak 5-HTP plasma levels were *lower* than the stable

5-HTP plasma levels resulting from 5-HTP SR 100 mg/kg/day. Recently we found that *oral* adjunct 5-HTP SR ~1000 mg/kg/day enhances brain 5-HT and plasma 5-HTP levels, and by extension 5-HT_{Ext}, several-fold stronger than 5-HTP SR via minipumps, and, again, with no adverse events (Jacobsen et al, unpublished). Thus, in our model systems, as compared to 5-HTP IR, 5-HTP SR potently and safely elevates 5-HT_{Ext} beyond the SSRI effect, and allows for higher safe 5-HTP exposure. While the contrast may be less stark in the clinic, our mouse data provide proof-of-principle of the therapeutic superiority of 5-HTP SR compared to 5-HTP IR.

Concluding Remarks

Antidepressant drug discovery is hampered by the poor predictability of animal "antidepressant-like" behavioral models [84]. Optimally, the rationale for a novel antidepressant should rest on strong clinical, as well as pre-clinical, data. The adjunctive 5-HTP SR therapeutic concept for TRD is founded in 5-HT biology, 5-HTP clinical and pre-clinical pharmacology, pharmacokinetics, and promising clinical pilot trials in TRD with 5-HTP and four other serotonergic adjuncts. In addition, we have shown in mice that chronic adjunctive 5-HTP SR safety and robustly elevates 5-HT_{Ext} beyond what is achieved by an SSRI, i.e. an antidepressant augmentation-like effect. As 5-HTP pharmacology appears similar between rodents and humans, we expect our mouse data will translate to humans. Based on previous clinical data, we project the therapeutic dose of adjunct 5-HTP SR will be 500–2000 mg per day [45]. Given the pharmacokinetics, physiochemical properties, and projected dose, realizing a 5-HTP SR formulation drug will be technologically feasible [85]. Many important drugs are specialized formulations of naturally occurring APIs [86, 87]. The ideal 5-HTP SR drug would produce essentially stable 5-HTP plasma levels at once or twice daily dosing. Defining the pharmacology of 5-HTP SR in clinical and preclinical paradigms opens a new line of inquiry (see Outstanding Questions Box). Indices of 5-HT deficiency segregate with suicidality, severe depression, and co-morbid borderline personality disorder, factors that predict poor SSRI treatment response (reviewed in [21]). Conceivably, adjunct 5-HTP SR will be particularly relevant for such patient populations. SSRIs are also approved for, but only partially effective in, *OCD*, *PTSD*, *social anxiety*, *panic disorder*, and *generalized anxiety*. Adjunctive 5-HTP SR could be therapeutically relevant also for these large indications. Further, a 5-HTP SR drug might also be effective as monotherapy, as an alternative to existing antidepressants.

In closing, strong data support that a high-performing adjunctive 5-HTP SR drug will be safe and effective in patients with depression, and potentially with other CNS indications, who fail to achieve adequate benefit from SERT inhibitor monotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

5-hydroxytryptamine (5-HT, aka serotonin)
Signaling molecule in CNS and periphery

Extracellular 5-HT (5-HT_{Ext})
The "active" 5-HT pool signaling via 5-HT receptors

5-hydroxytryptophan immediate-release (5-HTP IR)
Standard, native 5-HTP

5-hydroxytryptophan slow-release (5-HTP SR)
Concept wherein 5-HTP is delivered as SR. In rodents 5-HTP SR can be modeled using minipumps or dietary administration

Active pharmaceutical ingredient (API)
The compound in a dosage form/drug exerting the pharmacological action

Adverse event
Undesirable experience associated with use of a medical product

Blood-brain barrier (BBB)
Selective permeability barrier separating CNS extracellular fluid from the blood

Cerebrospinal fluid (CSF)
Brain and spine extracellular fluid

C_{Max}
The peak concentration of the API following administration

Depression
Mental disorder characterized by persistent feelings of sadness and loss of interest, together with additional symptoms, such as guilt, loss of energy, or suicidal ideation

Discontinuation syndrome
Can occur when 5-HT_{Ext}-elevating antidepressants are stopped abruptly. Core symptoms include dizziness, nausea, lethargy, and headache

Exposure
The API (concentration X time) area-under-the-curve after administration

Hamilton depression (HAMD) scale
A multi-dimensional tool to create an aggregate score of depression severity

Immediate-release
The dosage form delivers the entire API dose instantly

Peripheral amino acid decarboxylase inhibitor (DCI)
Penetrates the BBB minimally, and therefore inhibits conversion of 5-HTP to 5-HT only peripherally. DCI co-administration increases 5-HTP brain exposure 5- to 15-fold and doubles the $T_{1/2}$

Pharmacokinetics
The study of how the body disposes of an API

Pharmacodynamics
The study of what the API does to the body

Selective serotonin-reuptake inhibitors (SSRIs)
Class of drugs that at therapeutic levels selectively inhibits the SERT (see below)

Serotonin syndrome
Toxic syndrome caused by excessive $5\text{-}HT_{Ext}$ and characterized by neuromuscular excitation (e.g. clonus), autonomic excitation (e.g. hyperthermia), and altered mental state (e.g. agitation)

Serotonin transporter (SERT)
Transports back into the neuron cytosol 5-HT released via vesicles to the extracellular space

SERT inhibitor
Drug that inhibits the SERT. Includes the SSRIs, dual serotonin-noradrenaline reuptake inhibitors (SNRIs), and certain tricyclic antidepressants, e.g. clomipramine

Slow-release (SR) formulation
The dosage form delivers the API dose gradually. The result is reduced C_{Max}, delayed T_{Max}, and increased $T_{1/2}$. For APIs with $T_{1/2} < 12h$, a SR formulation often increase overall clinical effectiveness, by decreasing C_{Max}-related onset adverse events, producing a sustained pharmacodynamics effect, and decreasing dosing frequency

$T_{1/2}$
The terminal elimination half-life of an API, measured after absorption is complete

T_{Max}
The time to C_{Max} after dosing

Treatment-resistant depression
Typically defined as failure to achieve remission with two or more adequate courses of antidepressants

Tryptophan depletion
Acute administration of a tryptophan-devoid amino acid drink competes out uptake of tryptophan via brain amino-acid transporters. The result is an acute drop in brain 5-HT synthesis and in $5\text{-}HT_{Ext}$ (when elevated due to SERT inhibition)

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Box 1

5-HTP facts

- *Stereochemistry:* The natural occurring stereoisomer of 5-HTP is L-5-HTP.
- *Source:* Exogenous 5-HTP is usually extracted from the African shrub *Griffonia Simplicifolia.*
- *Regulatory status:* In the USA 5-HTP is regulated as a food supplement. There is no FDA-approved drug on the market containing 5-HTP as an active pharmaceutical ingredient. To our knowledge, no dosage form of 5-HTP has ever been formally developed as a drug and approved by a regulatory body for the treatment of a disease.
- *5-HTP absorption, distribution, metabolism, and excretion:* No other metabolic fate for 5-HTP than decarboxylation to 5-HT is known. In humans, upon oral administration, 5-HTP is rapidly absorbed from the upper intestine, with a T_{Max} of 1.5h [60]. Elimination is equally rapid, with a $T_{1/2}$ of 2h [60, 89]. The human bioavailability of 5-HTP, when given alone, has not been determined. Whether 5-HTP is passively or actively absorbed is also not known, although, based on rat studies [90], it seems likely that luminal amino acid transporters, also involved in L-DOPA absorption, play a role. In contrast to 5-HT, which does not, 5-HTP crosses the blood-brain barrier, as assessed using radiolabeled 5-HTP tracers [91]. After oral administration of 5-HTP, e.g. of 300 mg/day [92], enough 5-HTP enters the brain to enhance 5-HT synthesis, as assessed by an increase in cerebrospinal fluid levels of 5-HIAA, the major 5-HT metabolite. When 5-HTP is co-administered with a peripheral amino acid decarboxylase inhibitor (DCI) - which reduces peripheral, but not brain, metabolism of 5-HTP - 5-HTP exposure is increased 5 to 15-fold, the $T_{1/2}$ doubled to 4h, and bioavailability is 70% [93]. A few studies have examined the disposition of 5-HTP in animals. In rats, *Shindo et al* reported that 5-HTP is completely absorbed from the jejunum lumen via an active mechanism. 5-HTP transport into the brain also involves active transport. 5-HTP metabolism in the intestine and liver is 3 and 7 times slower, respectively, as compared to L-DOPA [90]. Such slower metabolism could account for the observed longer human $T_{1/2}$ of 5-HTP (2h) vs. L-DOPA (1h) [94]. In mice, in a study discussed in the main text, we determined the $T_{1/2}$ to be about 12 min [83], 10 times faster than in humans, in accordance with the typical mouse:human metabolism and dose-extrapolation scaling factor of about 10 [95].

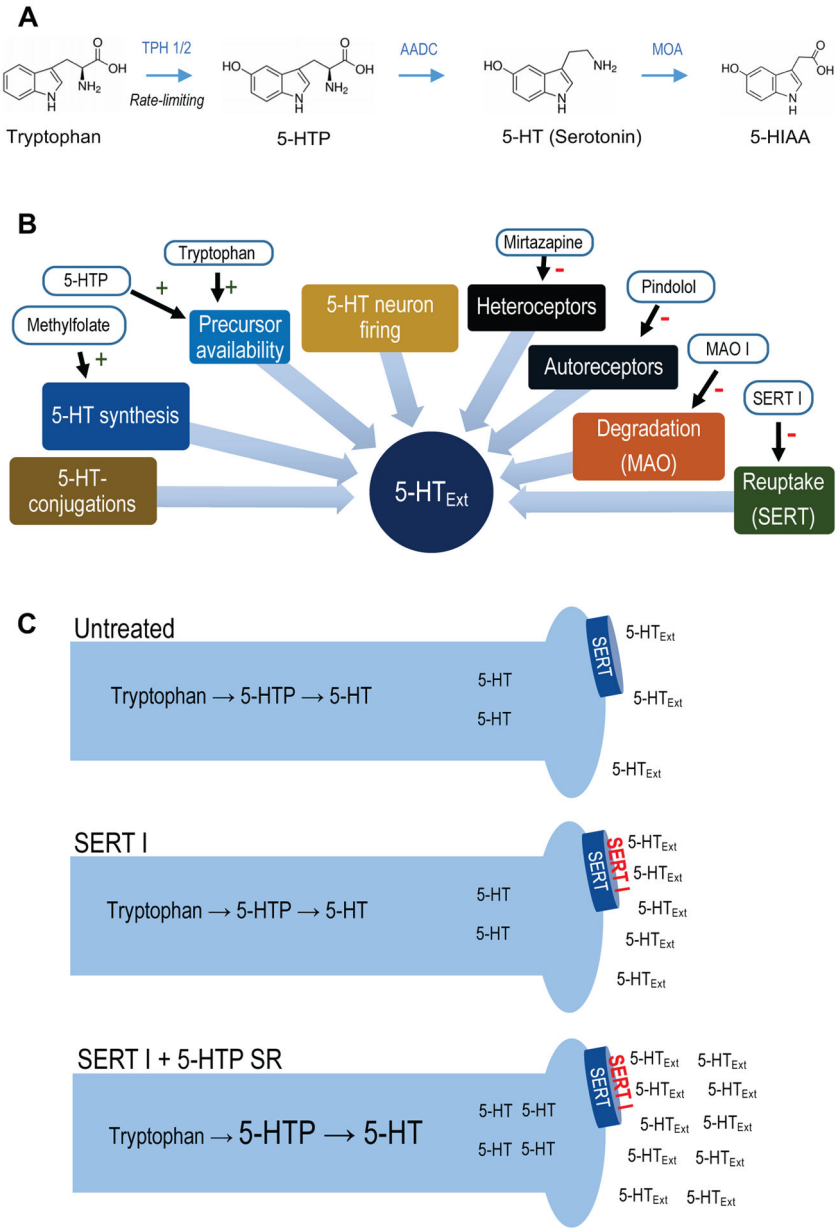

Figure 1.

(**A**) 5-HT metabolic pathway. Synthesis of 5-HTP from tryptophan via TPH 1 (periphery) or TPH 2 (CNS) is the rate-limiting step in 5-HT synthesis. 5-HTP is rapidly converted to 5-HT by the ubiquitous enzyme amino acid decarboxylase. 5-HT is metabolized to 5-HIAA, 5-HT's main metabolite, by monoamine oxidase. (**B**) Simplified schematic of regulatory elements of CNS 5-HT_{Ext}. Drugs interacting with each element are indicated. (**C**) Schematic for adjunct 5-HTP SR mechanism-of-action. Adjunct exogenous 5-HTP increases endogenous 5-HT synthesis, increasing availability of 5-HT for net release by concomitant SERT inhibitor treatment. *Abbreviations*: 5-HT, 5-hydroxytryptamine (serotonin); 5-HT_{Ext}, extracellular 5-HT; 5-HTP, 5-hydroxytryptopan; 5-HIAA, 5-hydroxyindoleacetic acid; AADC, amino acid decarboxylase; MOA, monoamine oxidase; MOA I, monoamine oxidase

inhibitor; SERT, serotonin transporter; SERT I, serotonin transporter inhibitor; SR, slow-release; TPH, tryptophan hydroxylase.

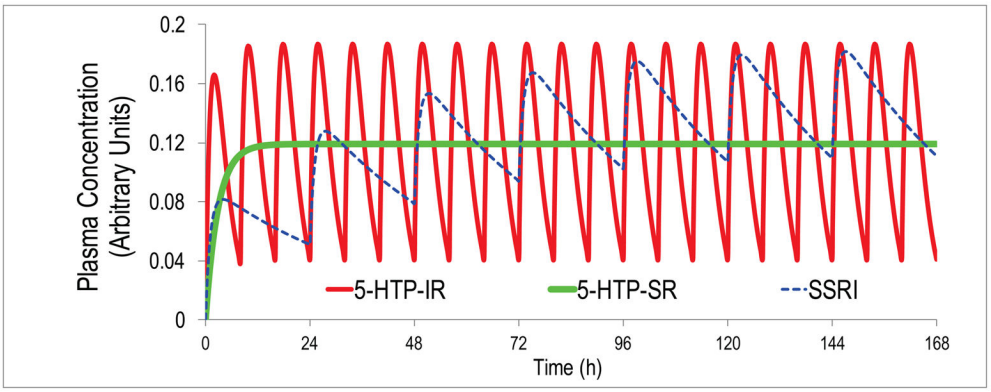

Figure 2.

Pharmacokinetics (PK) simulation using one-compartment modeling and published human PK parameters for 5-HTP IR [60] and the canonical SSRI escitalopram [88]. Even at thrice-daily dosing at 8h intervals, an unrealistic level of adherence in outpatients, 5-HTP plasma levels will fluctuate 5-fold between doses. In contrast, during steady-state once-daily dosing of escitalopram, plasma escitalopram levels will fluctuate only about 0.3-fold. Also shown are 5-HTP plasma levels obtained during steady-state dosing with an ideal 5-HTP SR dosage form producing zero-order, constant, 5-HTP delivery.

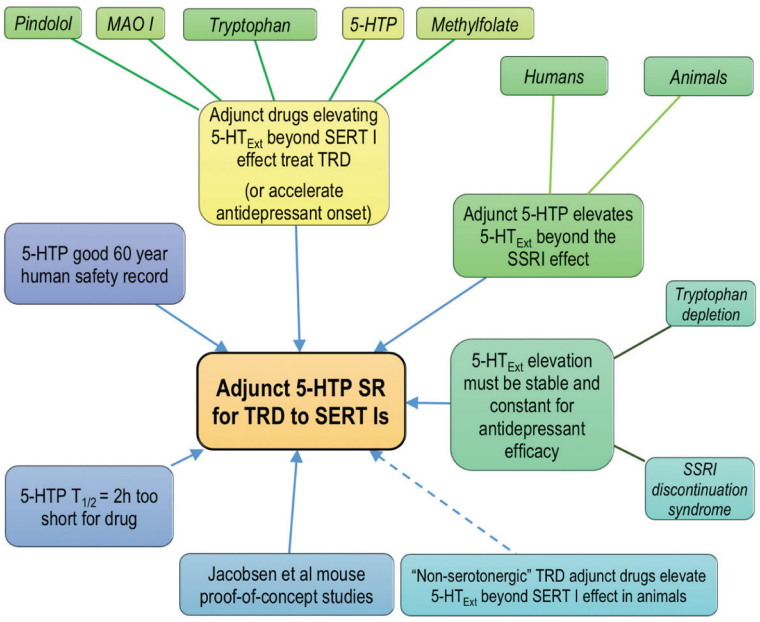

Figure 3.

Schematic summarizing the multi-pronged clinical and pre-clinical data converging on adjunct 5-HTP SR as a new therapy for treatment-resistant depression (TRD). SERT I, serotonin transporter inhibitor.

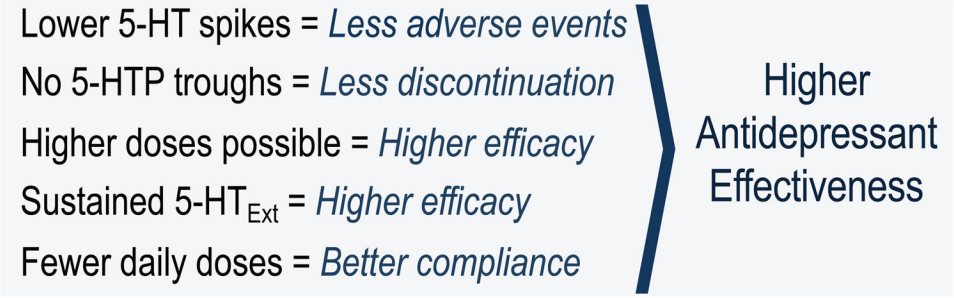

Figure 4.
Theoretical and experiential superiority of 5-HTP SR vs. 5-HTP IR.

Table 1

Clinical trials with adjunct 5-HTP immediate release in treatment-resistant depression

Reference	Design	Arms & total daily dose	Dosing	DCI	Duration	Population	Finding	Safety	Comment
Alino et al 1976 [34]	Double-blind; HAMD	Nialamide (MAO I) 200 mg (N=15) *vs.* Nialamide + 5-HTP 200 mg (N=15)	BID, at breakfast and lunch	None noted	15 days	Inpatients	Nialamide + 5-HTP superior ($p<0.05$) to Nialamide at day 15	2 patients in Nialamide + 5-HTP arm reported diarrhea	Doses of both drug titrated up over 5 days.
Hiele 1980 [35]	Open-label	Tricyclics (mostly) + 5-HTP (~200 mg/day) (N=99)	TID	Carbidopa, 150 mg/day	Variable	Outpatients; treatment-resistant on average for 18 months	50% of patients full recovery	Transient hypomania in 1/3; “no significant side-effects”	Patients resistant to multiple drug treatments; dichotomous all-or-none response to adjunct 5-HTP
van Praag et al 1982 [36]	Double-blind; HAMD	Placebo *vs.* clomipramine 225 mg (tricyclic) *vs.* HTP 200 mg *vs.* clomipramine + 5-HTP (N=10, all groups)	TID	Carbidopa, 150 mg/day, 5-HTP groups only	21 days	Inpatients	Both clomipramine and 5-HTP superior to placebo; clomipramine + 5-HTP superior to 3 other groups	Nausea	5-HTP doses titrated up
Nardini et al 1983 [37]	Double-blind; HAMD	Clomipramine 50 mg (tricyclic) (N=13) *vs.* clomipramine + 5-HTP (300 mg/day) (N=13)	?	None noted	28 days	Inpatients	Clomipramine + 5-HTP superior ($p<0.05$) to Clomipramine at day 28	Few adverse effects	No details on dosing regimen