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Enclosure:

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Symptoms of Major Depressive Disorder in Adults That Potentially Benefit From the Digital Therapeutic CT-152

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Introduction

- Digital therapeutics (DTx) may address unmet needs for patients with major depressive disorder (MDD), including increasing access to treatment and having fewer side effects than traditional antidepressant medications.[1–8] This access may be particularly important for patients with comorbid psychiatric symptoms or disorders, due to risk of drug-drug interactions and potential for additional side effects.[5,7]
- Based on the efficacy and favorable safety profile demonstrated in the pivotal Mirai trial (NCT04770285),[9] CT-152 received FDA 510(k)-clearance as a prescription DTx adjunct to antidepressant medication in patients with MDD symptoms.
  - The primary endpoint of Mirai was change from baseline in the Montgomery–Åsberg Depression Rating Scale (MADRS) at Week 6.[9]
    - The MADRS is a 10-item scale, rated from 0–6 (best–worst), with entries for: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts.
    - Although the MADRS is commonly utilized for determining efficacy during clinical trials, MDD is a heterogeneous disorder often presenting with different key symptomology depending on the patient.[10]
  - Symptom clusters have been suggested for the MADRS to aid with interpretation.[10] These clusters are evidence-based groupings designed to align and aggregate MADRS line items with key symptoms of depression.[10]
    - Clusters include responses for a range of symptoms associated with MDD.[10]
    - Each symptom cluster is comprised of an aggregation of the MADRS line items that most closely pertains to the symptom described (**Figure 1**.).[10]
- To better understand which symptoms of depression CT-152 may target, this post hoc analysis explored the role of baseline participant characteristics on clinical outcomes and assessed the clinical efficacy of CT-152 in improving MADRS symptom clusters and line items.

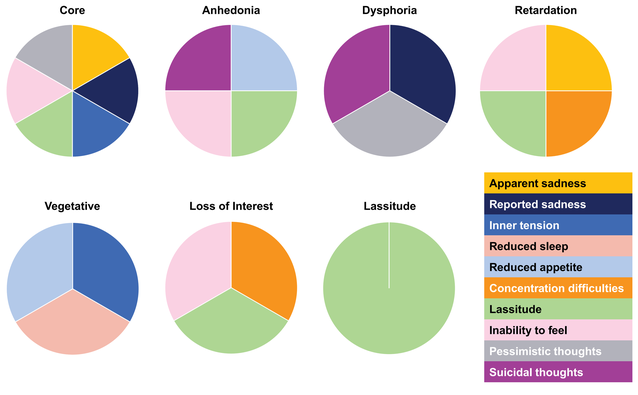
Methods

- Adults aged 22–64 years with a primary diagnosis of MDD (based on criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) with inadequate response to their current antidepressant medication were enrolled in the Mirai phase 3 trial, which included a 6-week intervention period to assess treatment efficacy and 4-week extension to assess treatment durability.[9]
- Participants were randomly assigned 1:1 to either treatment with CT-152 or sham[9]
  - Delivered via a smartphone app, CT-152 includes 3 components:
    1. Cognitive-emotional training (Emotional Faces Memory Task [EFMT]),
    2. Brief cognitive-behavioral therapy (CBT)-based lessons to reinforce and apply therapeutic skills, and
    3. Personalized text messages.[9]
  - The control group received a sham app that included a Shapes Memory Task (SMT), which is a working-memory task designed to match the EFMT for time and attention for task completion, but is not intended to be therapeutic and did not contain the CBT-based lessons.
  - All participants continued their current antidepressant medication, and both groups received supportive text messages to encourage treatment completion.[9]
- In the primary analysis, the main efficacy outcome was change from baseline in MADRS at Week 6. To further explore the effectiveness of CT-152 in treating symptoms of depression, we examined change in MADRS for subgroups of participants with baseline psychiatric symptomology as determined from MADRS symptom clusters, line items, and common clinical scales in this post hoc analysis.
  - Symptom clusters were identified from the literature, and are designed to help with interpretation of the 10-item clinician-reported MADRS in clinical practice.[10]
    - Clusters include responses for core, anhedonia, dysphoria, retardation, vegetative, loss of interest, and lassitude.[10]
    - Because each individual line item in the MADRS has a score range from 0–6 (best–worst), symptom cluster score maximums are 6 times the number of line items included in the respective cluster.
  - Between-group comparisons focused on change from baseline in MADRS for the CT-152 and sham groups for MADRS symptom clusters, because these are more relevant in clinical practice, with additional analyses using the MADRS line items.
- Correlations (Pearson's *r*) were explored between clinical outcomes (ie, change from baseline in MADRS total score at Week 6) and baseline demographic characteristics and psychiatric evaluation scores.
- Clinical efficacy was assessed as change in MADRS symptom clusters (eg, anhedonia, dysphoria) and line items at Week 6 compared with sham among all participants.
  - Outcomes were analyzed with mixed models for repeated measures, excluding trial site, which has been previously shown to have no significant influence on outcomes.
    - *P* values for post hoc analyses were not adjusted for multiplicity, are not powered, and are provided solely to help interpret findings.

Results

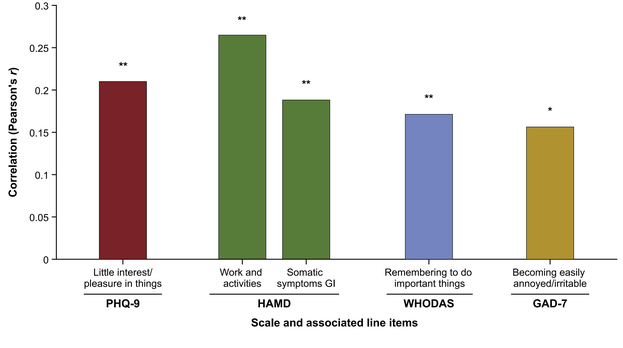
- Participants (N = 386) were randomly assigned to CT-152 (n = 194; 165 completed the trial) or sham (n = 192; 164 completed the trial).
- In single-arm comparisons:
  - Baseline correlations with psychiatric line items from clinical scales (Patient Health Questionnaire 9-item [PHQ-9], Hamilton Depression Rating Scale [HAMD], World Health Organization Disability Assessment Schedule 2.0 [WHODAS], Generalized Anxiety Disorder 7-Item [GAD-7]), showed correlations with MADRS change from baseline to Week 6 ($P < 0.1$), but the correlations were small (0.13–0.28), regardless of scale or line item (line items with at least $P < 0.1$; **Figure 2**).
  - Notable improvements in MADRS at Week 6 were observed for those who reported symptomology at baseline on items "becoming easily annoyed/irritable" from the GAD-7 ($P < 0.1$), and "little interest/pleasure in things" from the PHQ-9, "work and activities" and "somatic symptoms-GI" from the HAMD, and "remembering to do important things" from WHODAS ($P < 0.05$); however, correlations were small (0.16–0.26; **Figure 2**).
- Compared with sham, all 7 MADRS symptom clusters showed numeric improvement in the CT-152 group at Week 6.
  - Notable improvements were observed in core, anhedonia, retardation, loss of interest ($P < 0.1$), and vegetative ($P < 0.05$) clusters (**Figure 3**).
- Compared with sham, 9 out of 10 MADRS line items showed numeric improvement in the CT-152 group at Week 6.
  - Notable improvements were observed for items "reported sadness" ($P < 0.1$), and "reduced sleep" and "inability to feel" ($P < 0.05$; **Figure 4**).

Figure 1. MADRS symptom clusters as defined from respective combinations of line items[a]



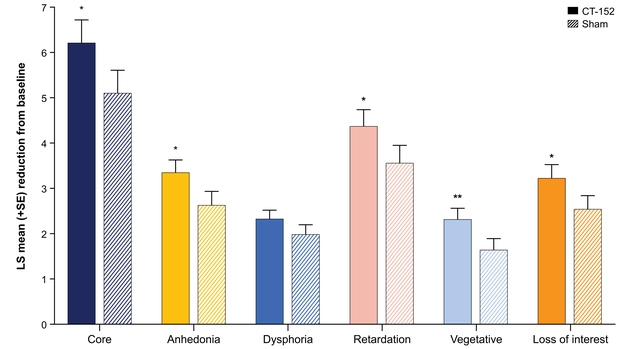
[a]Because each individual line item in the MADRS has a score range from 0–6 (best–worst), symptom cluster score maximums are 6 times the number of line items included in the respective cluster. Reproduced from Katzman MA et al. *J Affect Disord.* 2022; 316:201-208.10
MADRS, Montgomery–Åsberg Depression Rating Scale.

Figure 2. Correlations (Pearson's *r*) of MADRS change from baseline with participant baseline symptomology at Week 6



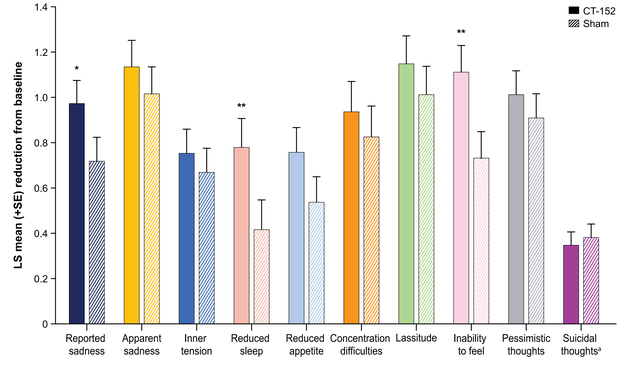
*$P < 0.1$ vs Baseline, not powered. **$P < 0.05$ vs Baseline, not powered.
GAD-7, Generalized Anxiety Disorder 7-Item scale; GI, gastrointestinal; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; PHQ-9, Patient Health Questionnaire 9-Item; WHODAS, World Health Organization Disability Assessment Schedule.

Figure 3. MADRS symptom cluster change from baseline in the CT-152 group versus sham at Week 6[a]



*$P < 0.1$ vs Sham, not powered. **$P < 0.05$ vs Sham, not powered.
[a]Lassitude is shown in Figure 4.
LS, least-squares; MADRS, Montgomery–Åsberg Depression Rating Scale; SE, standard error.

Figure 4. MADRS line item change from baseline in the CT-152 group versus sham at Week 6



*$P < 0.1$ vs Sham, not powered. **$P < 0.05$ vs Sham, not powered.
[a]From the primary analysis, in the CT-152 group, 3.21% (n = 6) reported clinically important suicidality (based on predefined protocol criteria) compared with 4.84% (n = 9) in the sham group.[11]
LS, least-squares; MADRS, Montgomery–Åsberg Depression Rating Scale; SE, standard error.

CONCLUSIONS

Regardless of symptom clusters at baseline, patients showed improvement in change from baseline in MADRS total score to Week 6, however there was no singular symptom or characteristic that benefited the most.

CT-152 showed numerical improvements compared with sham in adults with MDD for mood, sleep, and vegetative symptoms.

- These symptoms are common for patients with MDD and may be exacerbating factors that arise as part of the current depressive episode, or underlying comorbid conditions.
- Patients receiving CT-152 showed improvement on individual line items of the MADRS suggesting that the therapeutic action of CT-152 targets the common symptoms of depression.

These findings support the potential for broad therapeutic effectiveness of CT-152 across individual symptoms and different symptom clusters.

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At Otsuka, we hold a deep respect for the value of every mind. We will not rest until mental illnesses and brain diseases are approached with the same priority and urgency as our physical health and recognized as chronic diseases that warrant early, equitable, and accessible intervention for patients and caregivers everywhere.

Disclosures

JA, **ZZ**, **HJ**, and **TC** are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. **TP-S** was an employee of Click Therapeutics, Inc. at the time the study was conducted.