



SYSTEMATIC REVIEW

Trace amine-associated receptor 1 (TAAR1) agonism for psychosis: a living systematic review and meta-analysis of human and non-human data [version 1; peer review: 3 approved]

Spyridon Sifakis ^{1,2}, Virginia Chiochia ³, Malcolm R. Macleod ⁴, Charlotte Austin^{5,6}, Ava Homiar ^{5,6}, Francesca Tinsdeall ⁴, Claire Friedrich ^{5,6}, Fiona J. Ramage ⁴, Jaycee Kennett ^{5,6}, Nobuyuki Nomura^{1,2}, Olena Maksym⁴, Grazia Rutigliano⁷, Luke J. Vano⁷, Robert A. McCutcheon⁵⁻⁸, David Gilbert⁹, Edoardo G. Ostinelli ^{5,6,8}, Claire Stansfield¹⁰, Hossein Dehdarirad¹⁰, Damian Omari Juma¹¹, Simonne Wright ¹², Ouma Simple ¹², Olufisayo Elugbadebo¹³, Thomy Tonia³, Ioannis Mantas¹⁴, Oliver D. Howes^{7,15}, Toshi A. Furukawa ^{16,17}, Lea Milligan ¹⁸, Carmen Moreno¹⁹, Julian H. Elliott^{20,21}, Janna Hastings ^{22,23}, James Thomas ¹⁰, Susan Michie ²⁴, Emily S. Sena ⁴, Soraya Seedat¹², Matthias Egger³, Jennifer Potts^{5,6}, Andrea Cipriani^{5,6,8*}, Georgia Salanti^{3*}, Stefan Leucht^{1,2*}

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Abstract

Background

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We co-produced a living systematic review of controlled studies examining TAAR1 agonists in individuals (with or without psychosis/schizophrenia) and relevant animal models. Two independent reviewers identified studies in multiple electronic databases (until 17.11.2023), extracted data, and assessed risk of bias. Primary outcomes were standardised mean differences (SMD) for overall symptoms in human studies and hyperlocomotion in animal models. We also examined adverse events and neurotransmitter signalling. We synthesised data with random-effects meta-analyses.




Results

Nine randomised trials provided data for two TAAR1 agonists (ulotaront and ralmitaront), and 15 animal studies for 10 TAAR1 agonists. Ulotaront and ralmitaront demonstrated few differences compared to placebo in improving overall symptoms in adults with acute schizophrenia (N=4 studies, n=1291 participants; SMD=0.15, 95%CI: -0.05, 0.34), and ralmitaront was less efficacious than risperidone (N=1, n=156, SMD=-0.53, 95%CI: -0.86, -0.20). Large placebo response was observed in ulotaront phase-III trials. Limited evidence suggested a relatively benign side-effect profile for TAAR1 agonists, although nausea and sedation were common after a single dose of ulotaront. In animal studies, TAAR1 agonists improved hyperlocomotion compared to control (N=13 studies, k=41 experiments, SMD=1.01, 95%CI: 0.74, 1.27), but seemed less efficacious compared to dopamine D2 receptor antagonists (N=4, k=7,

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1. **Keiko Ikemoto** , The University of Tokyo, Tokyo, Japan
2. **Pramod Nair** , Flinders University, Adelaide, Australia
3. **Gavin P Reynolds** , Sheffield Hallam University, Sheffield, UK

Any reports and responses or comments on the article can be found at the end of the article.

SMD=-0.62, 95%CI: -1.32, 0.08). Limited human and animal data indicated that TAAR1 agonists may regulate presynaptic dopaminergic signalling.

Conclusions

TAAR1 agonists may be less efficacious than dopamine D2 receptor antagonists already licensed for schizophrenia. The results are preliminary due to the limited number of drugs examined, lack of longer-term data, publication bias, and assay sensitivity concerns in trials associated with large placebo response. Considering their unique mechanism of action, relatively benign side-effect profile and ongoing drug development, further research is warranted.

Registration

PROSPERO-ID:CRD42023451628.

Plain language summary

There is a need for more effective treatments for psychosis, including schizophrenia. Psychosis is a collection of mental health symptoms, such as hearing voices, that can cause distress and impair functioning. These symptoms are thought to be caused by changes in a chemical messenger system in the brain called dopamine. Currently used antipsychotic medications target brain receptors that respond to dopamine. They are not effective in some people and can cause uncomfortable adverse events, such as weight gain and movement disorders, especially with long-term use. A new type of drug is the trace amine-associated receptor 1 (TAAR1) agonists. These drugs act on different brain receptors that can affect the activity of the dopamine system, but do not directly bind to dopamine receptors.

We aimed to understand if TAAR1 agonists can reduce symptoms of psychosis, what adverse events they might have, and how they work. We did this by reviewing and collating all available evidence until November 2023. This is a “living” systematic review, so it will be regularly updated in the future.

We looked at both human and animal studies investigating TAAR1 agonists. Human studies suggested that two TAAR1 agonists (namely, ulotaront or ralmitaront) might have little to no effect on reducing symptoms of psychosis compared to placebo in people with schizophrenia. They seemed to cause fewer adverse events than current antipsychotics. Data from animal studies suggested that TAAR1 agonists had some positive effects but potentially smaller than other antipsychotics. There were little to no data from both human and animal studies about how TAAR1 agonists actually work.

From the current evidence we are uncertain about these results. With the ongoing development of new TAAR1 agonists, more evidence is needed to understand their potential role in the treatment of

psychosis.

Keywords

Antipsychotics, TAAR1, schizophrenia, clinical trials, preclinical studies, meta-analysis, systematic review, living evidence



This article is included in the [The Global Alliance for Living Evidence on aNxiety, depressiOn and pSychosis \(GALENOS\)](#) gateway.

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Competing interests: Andrea Cipriani received research, educational and consultancy fees from the Italian Network for Paediatric Trials, CARIPLO Foundation, Lundbeck, and Angelini Pharma. Toshi A. Furukawa reports personal fees from Boehringer-Ingelheim, Daiichi Sankyo, DT Axis, Kyoto University Original, Shionogi, and SONY, and a grant from Shionogi outside the submitted work; in addition, TAF has patents 2020-548587 and 2022-082495 pending, and intellectual properties for Kokoro-app licensed to Mitsubishi-Tanabe. Oliver D. Howes has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organised by Angellini, Autifony, Biogen, Boehringer-Ingelheim, Eli Lilly, Elysium, Heptares, Global Medical Education, Invicro, Janssen, Karuna, Lundbeck, Merck, Neurocrine, Ontrack/ Pangea, Otsuka, Sunovion, Recordati, Roche, Rovi and Viatrix/ Mylan. He was previously a part-time employee of Lundbeck A/v. Dr Howes has a patent for the use of dopaminergic imaging. In the last three years Stefan Leucht has received honoraria for advising/consulting and/or for lectures and/or for educational material from Angelini, Boehringer Ingelheim, Eisai, Ekademia, GedeonRichter, Janssen, Karuna, Kynexis, Lundbeck, Medichem, Medscape, Mitsubishi, Otsuka, NovoNordisk, Recordati, Rovi, Teva. Robert A. McCutcheon has received speaker/consultancy fees from Karuna, Janssen, Boehringer Ingelheim, and Otsuka, and is a director of a company that hosts psychotropic prescribing decision tools. Carmen Moreno received honoraria as a consultant and/or advisor and/or for lectures from Angelini, Compass, Esteve, Exeltis Janssen, Lundbeck, Neuraxpharm, Nuvelution, Otsuka, Pfizer, Servier and Sunovion outside the submitted work. Nobuyuki Nomura has received speaker fees from Eisai, Meiji Seika Pharma, Otsuka, and Sumitomo Pharma; and manuscript fees from Sumitomo Pharma. Edoardo G. Ostinelli has received research and consultancy fees from Angelini Pharma. No other competing interests were disclosed.

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Background

Antipsychotic medications constitute the cornerstone of treatment in psychosis^{1,2}. However, they are associated with high failure rates³ and multiple debilitating adverse events¹. Consequently, there is a critical need to develop more efficacious and safer medications for psychosis beyond the current antipsychotics that act as dopamine D₂ receptor antagonists. Despite efforts, drug discovery in psychosis has frequently failed to identify non-dopaminergic medications in recent years, with many drugs that showed promise in animal studies failing in clinical trials, highlighting a translational disconnect^{4,5}.

Trace amine-associated receptor 1 (TAAR1) agonism is a potentially emerging and novel mechanism proposed for treating psychosis⁶. Currently, two TAAR1 agonists, ulotaront (SEP-363856, TAAR1 agonist and serotonin 5-HT_{1A} receptor partial agonist) and ralmitaront (RO6889450, TAAR1 partial agonist), have been under clinical development, but recent clinical trials have had inconclusive findings despite showing promise in preclinical studies^{6–8}. Nonetheless, the volume of data on TAAR1 agonism is rapidly increasing, and additional compounds are undergoing preclinical development^{6,9–11}. There remains uncertainty regarding their effects, underlying mechanism of action, and potential role in the treatment of psychosis⁶.

Objectives

Therefore, we co-produced a living systematic review and meta-analysis of human and non-human studies to examine the efficacy, tolerability, and underlying mechanism of action of TAAR1 agonism for psychosis. Within the GALENOS project¹², we are committed to co-production and believe that including those with lived experience (“experiential advisors”) in developing this review will increase the relevance of findings^{13,14}. In the first iteration, we focused on evidence from controlled human and non-human studies comparing TAAR1 agonists with placebo conditions or currently licensed antipsychotics.

Methods

This report refers to the first iteration of a living systematic review conducted within the GALENOS project¹². We used the PRISMA statement for reporting the systematic review (PRISMA 2020)¹⁵ and searches (PRISMA-S)¹⁶ and the GRIPP-2 short form¹⁷ for reporting Patient and Public Involvement (checklists in [extended data](#)).

The protocol of the living review was published in Wellcome Open Research¹⁸, and registered with PROSPERO (CRD42023451628) and Open Science Framework (<https://doi.org/10.17605/OSF.IO/86Z2P>). Adaptations and deviations from protocol, and more detailed descriptions of methods are reported in [extended data](#).

Living review methodology

We employ a living review approach, as detailed in our protocol¹⁸, due to the ongoing development and research on

TAAR1 agonists^{6,9–11}. We conduct searches and screen new data every three months. However, there was a three-month delay in searching for non-human studies due to the extensive volume of data in the initial search (see “Study identification”). Additionally, we are developing methods to automatise these processes. Review updates will be initiated upon identifying new data that could materially alter previous findings. Independently of the publication of the review findings and with sufficient human and non-human data, a multidisciplinary expert panel reviews the synthesized evidence in a triangulation meeting, and subsequently experiential advisors set future research priorities, as outlined within the GALENOS project¹². Decisions regarding the modification of review questions, methods or the cessation of the living mode will be made considering the outcomes of the triangulation meeting and research prioritization exercises.

Eligibility criteria and outcomes

Eligibility criteria

We included human and non-human controlled experimental studies investigating TAAR1 agonists compared to placebo conditions or antipsychotics in individuals (with or without psychosis), and “animal models of psychosis” (i.e., laboratory methods of inducing psychosis-like features and behaviours in animals), respectively. We used broad eligibility criteria enabling a comprehensive and streamlined data synthesis from both human and non-human studies. A more detailed description of study eligibility criteria and outcomes can be found in [extended data](#).

Regarding human studies, we decided *post hoc* to focus on randomised controlled trials (RCTs), but we also considered uncontrolled experimental studies on neurobiological outcomes due to the limited available data from controlled studies.

Outcomes

In human studies, the primary outcome was the severity of overall psychosis symptoms measured by validated rating scales, such as the Positive and Negative Syndrome Scale (PANSS)¹⁹. Secondary outcomes included severity of symptom domains and response to treatment, dropouts due to any reason and adverse events, serious and specific adverse events frequently reported with psychotropics^{1,20}. We conducted separate analyses of efficacy outcomes for subpopulations based on diagnosis (e.g., schizophrenia, Parkinson’s Disease psychosis). We pooled the different populations for dropouts and adverse events, as no substantial differences are expected for these outcomes across populations²¹.

In non-human studies, primary outcomes included increased locomotor activity and impairment of prepulse inhibition of the acoustic startle reflex. These behavioural measures have some predictive validity in detecting antipsychotic effects^{4,22–25}. Secondary outcomes included other behavioural measures such as cognitive function, dropouts, and adverse events.

We also examined potential mechanistic insights by presenting narratively the findings from human and non-human studies

on measures of neurotransmitter signalling. Moreover, we investigated the effects of TAAR1 agonists compared to control in TAAR1-knockout animals to determine whether observed differences could be attributed to TAAR1 agonism.

Study identification

The search strategies were reported in [extended data](#). HD and CS conducted searches for human studies (until 17.11.2023) in PubMed/MEDLINE, Embase, International Pharmaceutical Abstracts, Web of Science, Biosis, PsychINFO, CENTRAL, OpenAlex, [clinicaltrials.gov](#), [WHO-ICTRP](#) and ScanMedicine. MRM and FR conducted searches for the non-human studies (until 28.08.2023) in PubMed, Scopus, Web of Science, and PsychINFO.

Study selection, data extraction and risk of bias evaluation

We used similar methods for study selection, data extraction, and risk of bias evaluation of human and non-human studies, which were conducted by two independent reviewers (SS, CA, CF, NN, JK, GR, LV for human studies; FT, FR, CA, CF, JK, OM and MRM for non-human studies) with reconciliation of discrepancies by senior authors (SS, RAM and SL for human studies; MRM for non-human studies). These processes for human studies were conducted in Evidence for Policy, and Practice Information and Coordinating Centre (EPPI-Reviewer)²⁶ and for non-human studies in Systematic Review Facility (SyRF)²⁷.

Data extraction process

We extracted data for study characteristics and outcomes. For continuous outcomes, we preferred change over endpoint scores, and data based on methods accounting for missing data. For dichotomous outcomes, we used the number of individuals/animals allocated to a group as denominator. For crossover studies, we opted to use data from the first phase²⁸. However, when only data from the entire trial duration were reported, we applied appropriate methods to correct the variance^{21,28}, assuming a correlation (i.e., $\rho=0.2$ for dropouts and adverse events). We extracted data from variations of the same outcome measure in non-human studies and synthesized them jointly (see “Data analysis”).

We extracted and analysed data at three prespecified timepoints: between 3 and 13 weeks (primary timepoint), shorter-term measurements spanning from immediate post-administration of the intervention to 3 weeks, and longer-term measurements beyond 13 weeks.

Risk of bias assessment

We evaluated risk of bias for all outcomes using the RoB2 tool for RCTs²⁹ and the SYRCLE’s tool for animal studies³⁰. Moreover, we assessed reporting completeness of animal studies using a modified ARRIVE Essential 10 checklist^{18,31}.

Data analysis

Data analysis was conducted separately for human and non-human studies (SS, and MRM, FR, FT, respectively, supervised by VC and GS). We analysed data comparing TAAR1

agonists versus inactive control conditions or antipsychotics in human and non-human studies, and TAAR1 agonists combined with antipsychotics versus antipsychotics alone in non-human studies.

Effect sizes

Effect sizes for continuous outcomes were standardised mean differences (SMDs) and mean differences for weight, prolactin levels, and QTc interval, and for dichotomous outcomes were odds ratios (ORs). We also used normalised mean differences (NMD) in sensitivity analysis of non-human studies if there were sufficient data for sham procedures ([extended data](#)). We presented effect sizes with 95% confidence intervals (95%CI).

Data synthesis approach

We synthesized data with meta-analysis whenever sufficient data were available from at least two independent effect sizes for the same outcome. Additionally, we presented effect estimates even when available data were only from a single human study. However, we did not consider such data further for non-human studies; the substantial heterogeneity observed in reviewing animal studies means the findings of a single study are of limited value.

We conducted random-effects meta-analysis for human studies using restricted maximum likelihood to estimate the between-study variance (τ^2). For non-human studies, we used a multilevel random-effects meta-analysis³² when there were at least 5 unique categories for at least one level. The three nested levels, from higher to lower, were animal strain, study record, and experiment ([extended data](#)). We used t-distributions, considering degrees of freedom for the multilevel model, to adjust the confidence intervals³³. To account for correlated sampling errors, we estimated the within-study variance-covariance matrix by assuming a correlation of $\rho=0.5$ ³² and clustering by publication.

Exploration of heterogeneity

Heterogeneity was quantified using 95% prediction intervals and, in human studies τ^2 , and presented when there were data from more than five studies to estimate the heterogeneity variance. For non-human studies, we reported the variance attributable to each of the nested levels. Potential sources of heterogeneity were explored in predefined meta-regressions¹⁸. The data were limited for human studies, but we provided pooled estimates for the primary outcome for the different TAAR1 agonists and doses. For non-human studies, we conducted meta-regressions for sex, induction method, drug characteristics, dose, timing of intervention, risk of bias, and reporting completeness (*post hoc*, [extended data](#)).

Sensitivity analyses

We examined the robustness of the findings with pre-defined sensitivity analyses, using: 1) fixed-effects meta-analyses of human studies (*post hoc*, due to small number of studies), 2) NMD in non-human studies, 3) different assumptions for sampling correlations ($\rho=0.2/0.8$) in non-human studies, and 4) robust variance estimation in non-human studies ([extended data](#))^{32,34}.

Reporting bias

We assessed reporting bias for all outcomes in human studies using the ROB-ME (risk of bias due to missing evidence) tool³⁵. We examined small-study effects with regression-based tests (extended data)^{32,36}, whenever data were available from at least 10 human or non-human studies.

Summary of the evidence

We assessed and presented within-study biases, across-study biases, indirectness, and other biases in predefined summary of evidence tables¹⁸.

Software

Data analysis was conducted in R statistical software v.4.3.1/2³⁷ using PRISMA2020 v1.1.1³⁸, robvis v0.3.0.900³⁹, tidyverse v2.0.0⁴⁰, meta v6.5-0⁴¹ (human studies), orchard v2.0⁴² and metafor 4.4-0³³ and (non-human studies). The complete list of packages can be found in detailed results reports (extended data).

Co-production methods

The review was co-produced by multiple stakeholders, including experiential advisors¹³. The topic was drawn from previous prioritisation exercises with patient and public involvement (for instance, James Lind Alliance), and experiential advisors were involved in designing the protocol, interpreting the findings, preparing plain language summaries and disseminating the findings to the wider public^{12,14}.

Results

The extended data included detailed reports with summary of evidence tables^{43,44}.

Findings from human studies

Study description

We screened 3962 titles/abstracts and 166 full texts (Figure 1). We included 25 RCTs, 20 completed (2147 participants) and 5 still ongoing on 20.01.2024 (extended data). There were usable data from 9 RCTs^{7,45–52} with 1683 adult participants (median of mean age 32.9 years, 69.8% men, 30.2% women) conducted by pharmaceutical industries (Table 1). These trials examined two TAAR1 agonists (ulotaront and ralmitaront). Five studies had parallel design examining the efficacy and tolerability of ulotaront^{7,45,50,51} or ralmitaront⁵² compared with placebo (i.e., inert substance) and/or risperidone⁵² over 4–6 weeks in acute schizophrenia^{7,50–52} or Parkinson's Disease psychosis⁴⁵. The other four trials had parallel or crossover design and examined treatment with ulotaront as single dose^{46,48,49} or up to 2 weeks⁴⁷. Additionally, we considered a single-arm neuroimaging study examining the effects of 2-week treatment of ulotaront on dopamine synthesis capacity in schizophrenia⁵³.

All of the RCTs had an overall low risk of bias according to RoB2, except for some concerns in one single dose crossover study⁴⁸, and a high risk in the study of Parkinson's Disease psychosis due to missing outcome data (extended data)⁴³.

Primary outcome

In participants with acute schizophrenia, TAAR1 agonists showed little difference compared to placebo in improving overall symptoms measured by PANSS total over a treatment of 4–6 weeks (number of studies N=4, number of participants n=1291, SMD=0.15, 95%CI: -0.05 to 0.34) (Figure 2A). The data were limited for conducting subgroup analyses, with no clear differences between effect sizes for ulotaront and ralmitaront, and no clear indications of dose-response relationships (Figure 2B). There were concerns of underestimation of the effects of ulotaront due to large placebo response (i.e., observed symptom improvement in the placebo groups) in two of the ulotaront trials^{50,51,54}. One RCT found that ralmitaront was less efficacious than the antipsychotic risperidone (n=1, N=156, SMD=-0.53, 95%CI: -0.86 to -0.20)⁵², and no other study directly compared TAAR1 agonists with antipsychotics.

In participants with Parkinson's Disease psychosis, one small study found no clear differences between ulotaront and placebo in improving overall symptoms at 6 weeks (n=1, N=37, SMD=-0.28, 95%CI: -0.95 to 0.38)⁴⁵.

Secondary outcomes

Secondary efficacy outcomes

The findings on response to treatment were in agreement with those of the primary outcome, showing no clear differences between TAAR1 agonists and placebo (extended data). There were limited data for other secondary efficacy outcomes including symptom domains.

Dropouts

TAAR1 agonists appeared to be associated with more dropouts due to any reason compared to placebo in participants with psychosis over treatment of 4–6 weeks. Still, the effects were small and imprecise (N=5, n=1396, OR=1.22, 95%CI: 0.93, 1.60) (Figure 3). There was no clear difference between TAAR1 agonists and placebo in dropouts due to adverse events (N=3, n=497; OR=1.15, 95%CI: 0.58, 2.29) (Figure 3). There was a moderate risk of missing evidence.

Adverse events

The data on adverse events were limited, often accompanied by imprecise estimates, and moderate risk of missing evidence or indirectness (extended data).

TAAR1 agonists did not appear to differ from placebo in adverse events in participants with psychosis at 4–6 weeks, including for serious adverse events, nausea/vomiting, QTc prolongation, weight increase, prolactin elevation, akathisia, extrapyramidal side-effects, sedation and insomnia, with absolute frequencies generally not exceeding 5% (Figure 3). Moreover, one RCT found that ralmitaront had fewer adverse events of any type than risperidone (OR=0.38, 95%CI: 0.21, 0.68), less nausea/vomiting (OR=0.16, 95%CI: 0.03, 0.84) or weight increase (OR=0.12, 95%CI: 0.02, 0.58) in 214 participants with acute schizophrenia⁵². A single dose of ulotaront, when

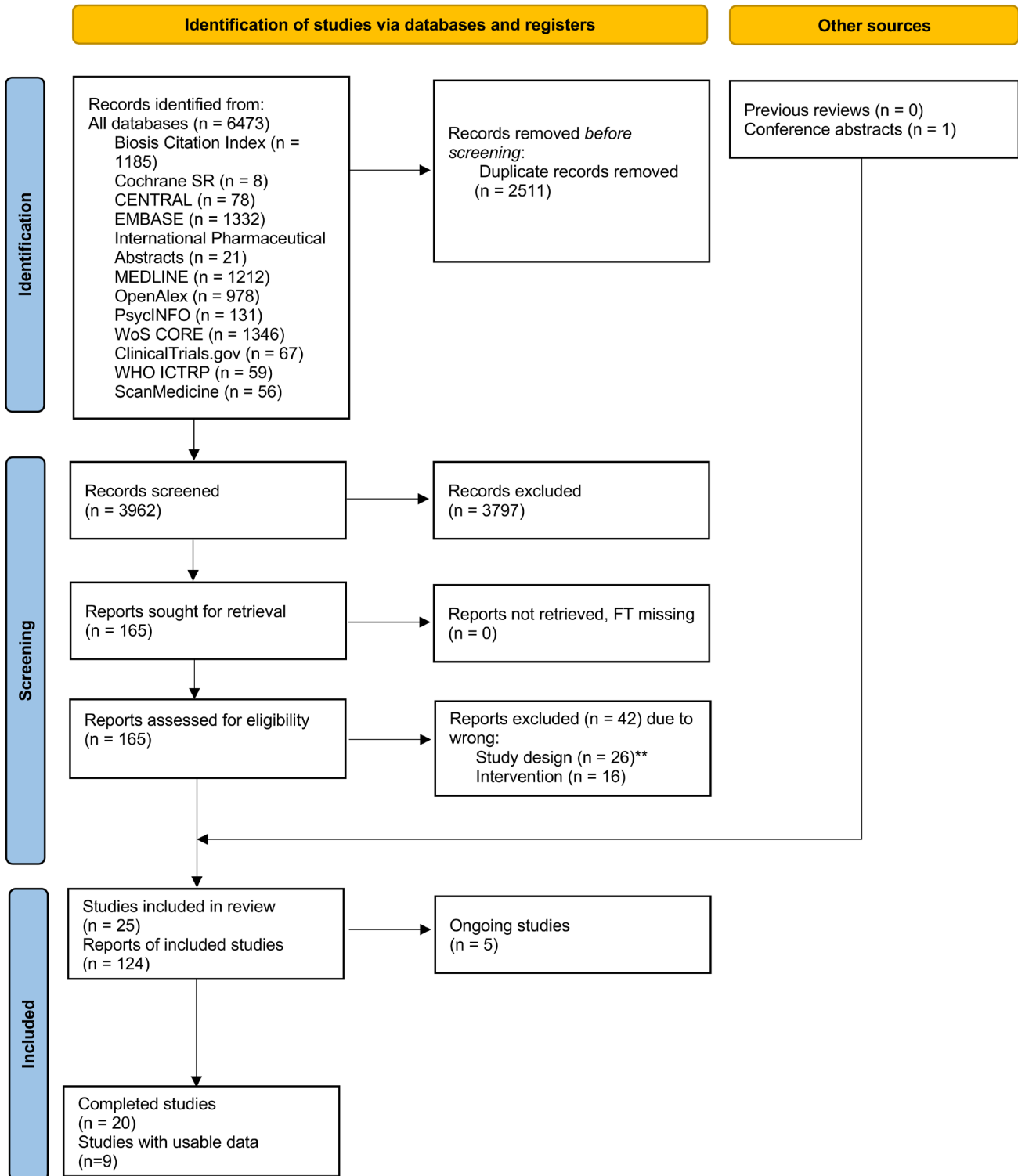


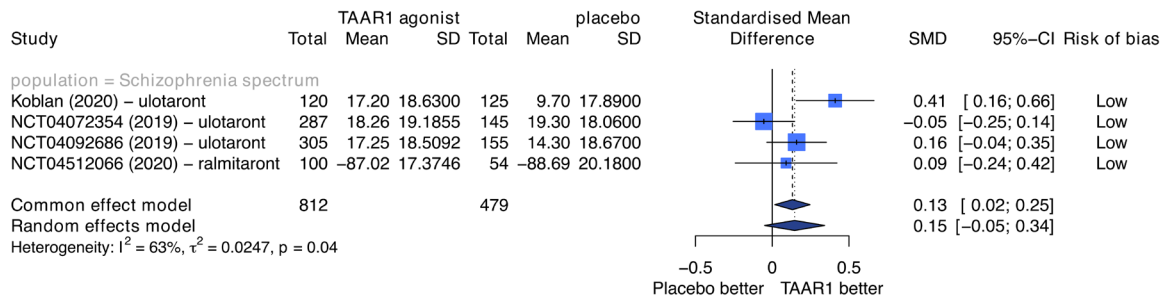
Figure 1. PRISMA flow diagram for study selection of human studies. **One single-arm neuroimaging study (NCT04038957) had originally been listed here as excluded, but its findings were *post-hoc* considered to provide mechanistic insights of the effects of TAAR1 agonists.

Table 1. Table of characteristics of human studies.

Study name	Study ID	Year	Design	Population	Intervention	Sample size	Objectives	Usable data
Hopkins <i>et al.</i> 2021 ⁴⁹	SEP361-103	2021	DB-RCT two-period crossover; single dose (phase 1)	Men 18-35 years	Cohort 1: Ulotaront 10mg; Placebo Cohort 2: Ulotaront 50mg; Placebo	24	Sleep parameters, pharmacokinetics	Dropouts, side-effects
Isaacson <i>et al.</i> 2023 ⁴⁵	SEP361-203, NCT02969369	2023	DB-RCT; 6 weeks (with open label extension) (phase 2)	Men/women ≥55 years with Parkinson's disease psychosis (acute)	Ulotaront 20-75mg/d; Placebo	39	Efficacy (acute), safety	Efficacy, dropouts, side-effects
Koblan <i>et al.</i> 2020 ⁷	SEP361-201, NCT02969382, EUCTR2016-001555-41	2018	DB-RCT; 4 weeks (with open label extension) (phase 2)	Men/women 18-40 years with schizophrenia (acute, DSM-5)	Ulotaront (50-75mg/d); Placebo	245	Efficacy (acute), tolerability	Efficacy, dropouts, side-effects
NCT04072354 ⁵⁰	SEP361-301, NCT04072354, EUCTR2019-000470-36	2023	DB-RCT; 6 weeks (phase 3)	Men/women 13-17 and 18-65 years with schizophrenia (acute, DSM-5)**	Ulotaront 50mg/d; Ulotaront 75mg/d; Placebo	463	Efficacy (acute), tolerability	Efficacy, dropouts
NCT04092686 ⁵¹	SEP361-302, NCT04092686, EUCTR2019-000697-37	2023	DB-RCT; 6 weeks (phase 3)	Men/women 18-65 years with schizophrenia (acute, DSM-5)	Ulotaront 75mg/d; Ulotaront 100mg/d; Placebo	462	Efficacy (acute), tolerability	Efficacy, dropouts
NCT04512066 ⁵²	BP41743, NCT04512066, JPRN-jRCT2031200288	2022	DB-RCT; 8 weeks (up to 48 weeks extension) (phase II)	Men/women 18-45 years with schizophrenia or schizoaffective disorder (acute, DSM-5)	Ralmitaront 45mg/d; Ralmitaront 150mg/d; Risperidone 4mg/d; Placebo	287	Efficacy (acute), tolerability	Efficacy, dropouts, side-effects
Perini <i>et al.</i> 2023 ⁴⁶	SEP361-104, NCT01972711	2015	DB-RCT; single dose (phase 1)	Men/women 18-45 years (high or low levels of schizotypy)	Ulotaront 50mg; Amisulpride 400mg; Placebo	105	fMRI	Dropouts, side-effects, fMRI (narratively)
Szabo <i>et al.</i> 2023 ⁴⁷	SEP361-108, NCT05015673	2015	DB-RCT three-period crossover; 2 weeks (phase 1)	Men/women 18-55 years with narcolepsy/cataplexy	Ulotaront 25mg; Ulotaront 50mg; Placebo	18	Sleep parameters, pharmacokinetics, tolerability	Dropouts, side-effects
Tsukada <i>et al.</i> 2023 ⁴⁸	SEP361-114, NCT04369391	2020	DB-RCT three-period crossover; single dose (phase 1)	Men/women 18-65 years with schizophrenia (stable, DSM-5)	Ulotaront 150mg; Placebo; Moxifloxacin 400mg (ineligible for the review)	68	QTc interval, tolerability, pharmacokinetics	Dropouts, side-effects
NCT04038957 ⁴³	SEP361-118, NCT04038957, 2019-000568-65	2023	Open single-arm study; 2 weeks (phase 1)	Men/women 18-65 year with schizophrenia (stable, DSM-5)	Ulotaront 50-75mg/d (add-on to current antipsychotic treatment)	22	F-DOPA PET	F-DOPA PET (narratively)

SB: Single-blind; DB: Double-blind; RCT: Randomized controlled trial. The list of eligible studies and a more detailed table of study characteristics can be found in the [extended data](#). * This study was a single-arm neuroimaging study that was included *post-hoc* to provide mechanistic insights of the effects of TAAR1 agonists. ** There were usable data only for the adult population.

A. Forest plot of TAAR1 agonist versus placebo on overall symptoms in acute schizophrenia



B. Effect sizes for each dose level of ulotaront or ralmitaront compared to placebo on overall symptoms in acute schizophrenia

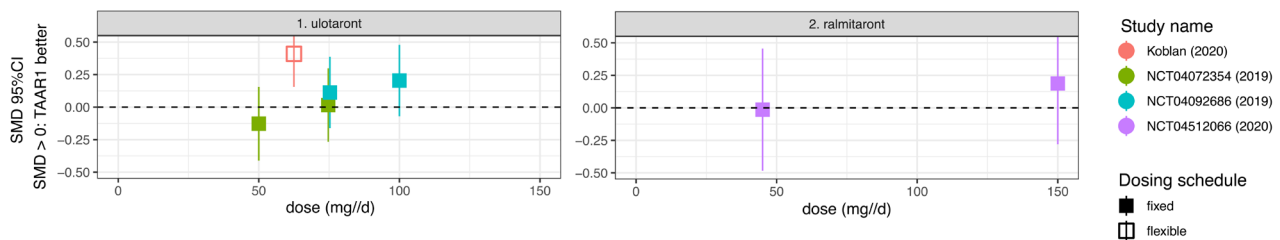


Figure 2. TAAR1 agonists versus placebo on overall symptoms in acute schizophrenia. A. Forest plot of TAAR1 agonists versus placebo on overall symptoms in acute schizophrenia. There were available data for ulotaront and ralmitaront. The findings of random- and fixed-effects meta-analyses are presented. The overall risk of bias according to RoB2 is also presented, with all studies having an overall low risk of bias. **B.** Effect sizes for each dose level of ulotaront and ralmitaront compared to placebo on overall symptoms in acute schizophrenia. The findings of each study are presented separately, and the effect sizes were corrected for using the same control in each study by subdividing accordingly the sample size. The study of Koblan *et al.* 2020 was a flexible dosing study, which used of ulotaront between 50 to 75mg/d and its effect size is placed in the middle of the range. SMD: Standardised mean difference, 95%CI: 95% confidence interval.

compared to placebo, was associated with nausea/vomiting (N=3, n=161, OR=15.14, 95% CI: 3.71, 61.75) and sedation (N=3, n=161, OR=9.55, 95% CI: 3.50, 26.09) in participants with schizophrenia or healthy volunteers, with absolute frequencies approaching 30% of participants (Figure 3).

Mechanistic insights

Two neuroimaging studies^{46,53} supported the notion that TAAR1 agonists can regulate dopaminergic signalling in the striatum (more details in extended data). One RCT indicated that a single dose of ulotaront may modulate striatal responses during the anticipatory phase of the Monetary Incentive Delay task using functional magnetic resonance imaging in 96 healthy volunteers⁴⁶. This task is related to reward processing and served as an indicator of heightened dopaminergic signalling⁴⁶. Another single-arm trial demonstrated that a 2-week treatment of ulotaront appeared to reduce striatal dopamine synthesis capacity measured with F-DOPA positron emission tomography (PET) (-3.98% from baseline; 95% CI: -8.68%, 0.72%) in 22 clinically stable participants with schizophrenia^{53,54}. This reduction correlated with the improvement in positive symptoms of psychosis^{53,54}.

Findings from non-human studies

Study description

We screened 1849 titles/abstracts and 20 full texts (Figure 4), ultimately including 15 studies⁵⁵⁻⁶⁹ (Table 2). These studies

encompassed multiple experiments involving 38 unique genetic or pharmacological methods to induce psychosis-like behaviours in rodents of various strains and sexes. The studies examined 10 different TAAR1 agonists (AP163, compound 50A, compound 50B, LK000764, RO5073012, RO5166017, RO5203648, RO5256390, RO5263397 and ulotaront), primarily administered as single doses in 84% of the cases, either individually or combined with antipsychotics. TAAR1 agonists were compared with control conditions similar to placebo in clinical trials (e.g., vehicle), and antipsychotics (i.e., aripiprazole, clozapine, olanzapine, and risperidone). The reporting quality according to the modified ARRIVE checklist was generally poor, resulting in unclear risk of bias assessments across most of the studies and the different domains of the SYRCLE’s tool (extended data).

Primary outcomes

TAAR1 agonists had overall positive and large effects compared to control conditions on locomotor activity in animal models of psychosis (N=13, number of experiments k=41; SMD=1.01, 95% CI: 0.74, 1.27) with point estimates of SMDs for individual compounds ranging from 0.46 for LK000764 to 1.61 for RO5256390 (Figure 5A). Some heterogeneity was observed, mainly attributed to between-experiment variance ($\tau^2=0.149$) and to a smaller degree to between-study variance ($\tau^2=0.054$). Higher doses of TAAR1 agonists appeared to be associated with higher efficacy in meta-regression

Summary forest plot of TAAR1 agonists versus placebo on dropouts and adverse events

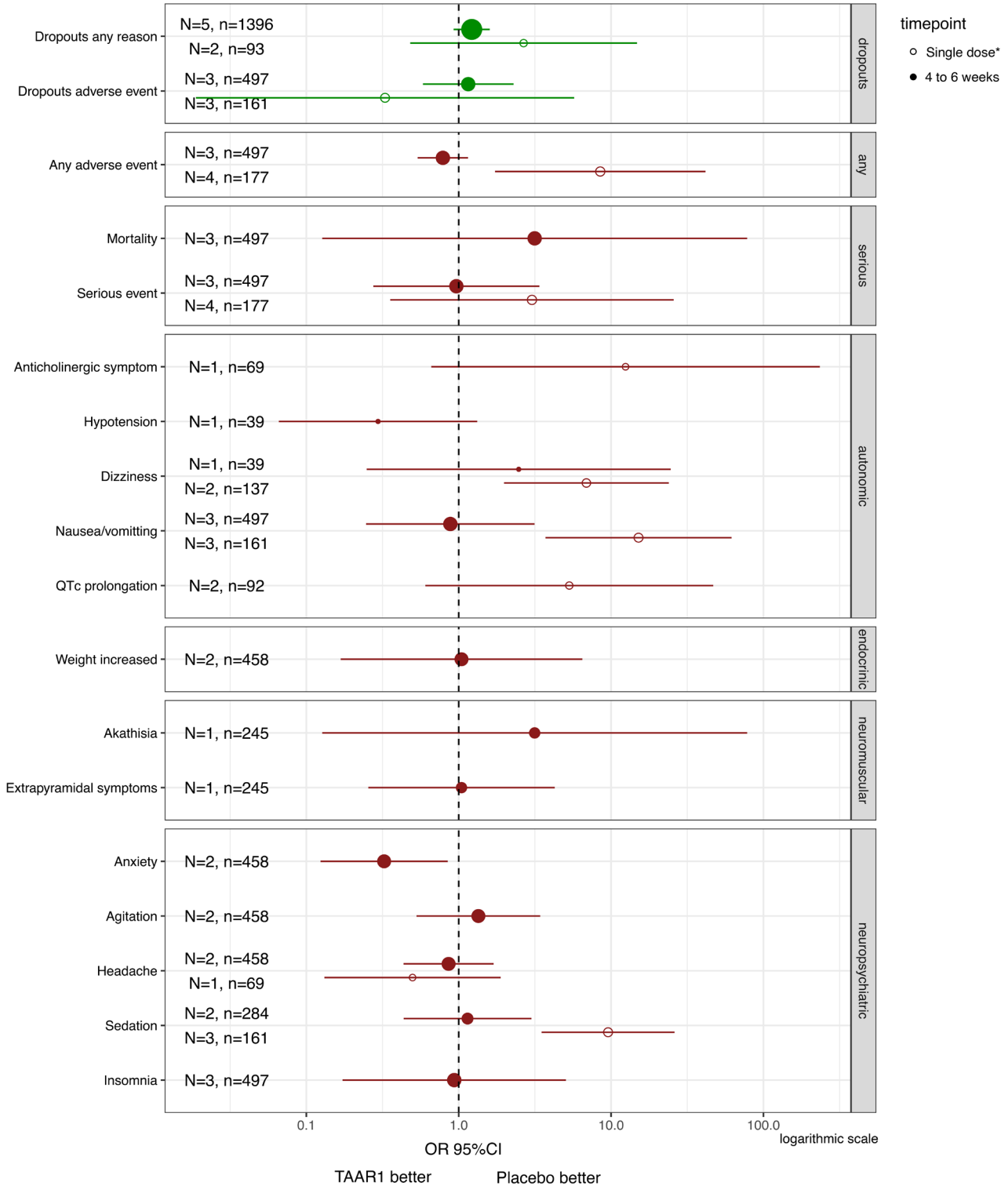


Figure 3. TAAR1 agonists versus placebo on dropouts and adverse events in human studies. Summary forest plot of TAAR1 agonists versus placebo on dropouts and adverse events. The pooled estimates from meta-analyses or effect sizes from single studies are presented for each of the outcomes relevant to dropouts and adverse events, separately for two timepoints with usable data. To ease the interpretation, adverse events were grouped in categories. There were usable data for treatment of ulotaront and ralmataront for 4 to 6 weeks in acute schizophrenia or Parkinson's disease psychosis, and after a single dose of ulotaront in participants with schizophrenia, healthy volunteers and narcolepsy-cataplexy. *This time point referred to events experienced after a single dose of ulotaront, except for additional and limited data for any and serious adverse events from the study by Szabo *et al.* 2023 examining treatment of 2 weeks with ulotaront. A logarithmic x-axis was used. N: number of studies; n: number of participants; OR: Odds ratio; 95%CI: 95% confidence interval.

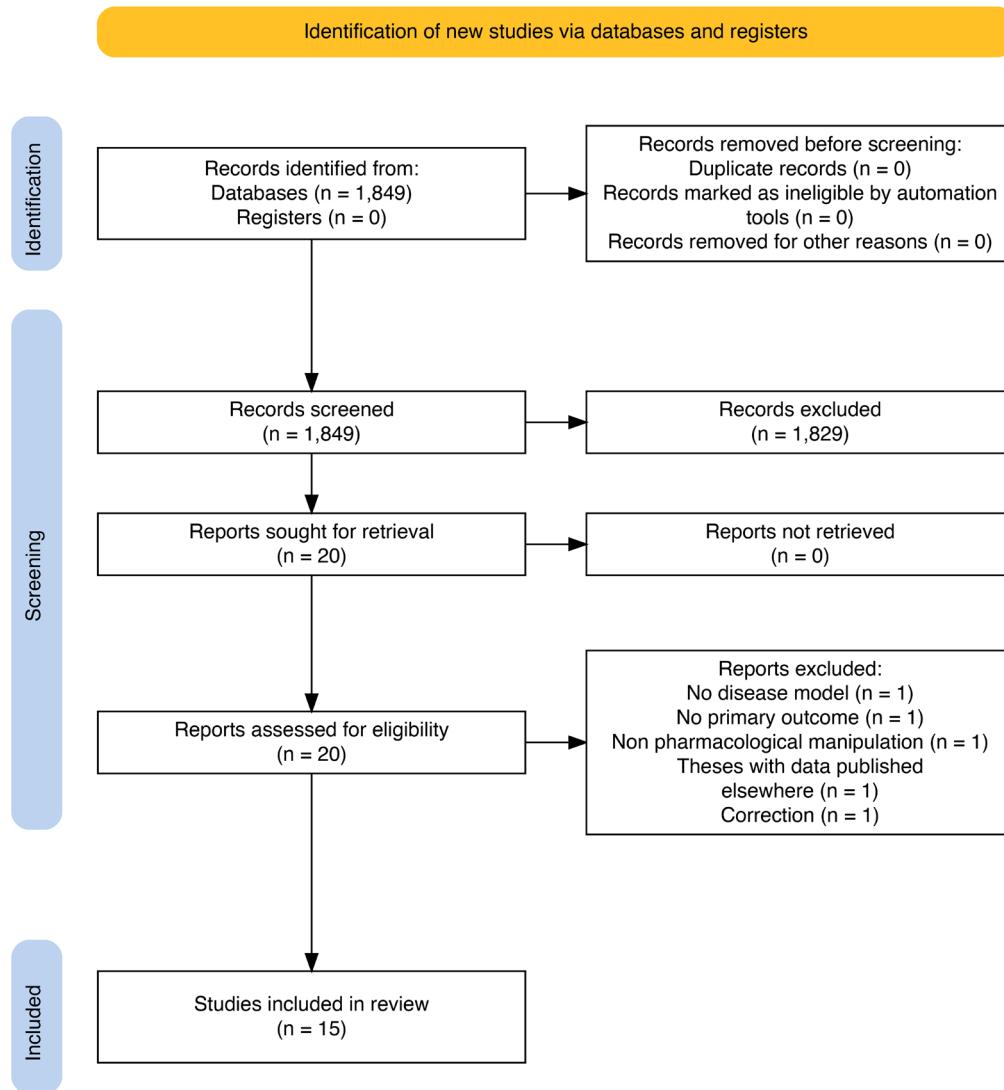


Figure 4. PRISMA flow diagram for study selection of non-human studies.

of dose standardized to the drug potency. An increase from doses reflecting 50% of the maximum efficacy to 80% was associated with an average increase in the effect size by 0.20 (95% CI: 0.15, 0.25) (Figure 5B). However, no dose-response effects were identified for ulotaront ($p=0.997$). The results were generally robust in sensitivity analysis, but study biases and small-study effects might have exaggerated effect sizes (extended data).

When compared to antipsychotics, TAAR1 agonists alone appeared to be less efficacious in improving locomotor hyperactivity ($N=4$, $k=7$, $SMD=-0.62$, 95% CI: -1.32, 0.08) (Figure 6). The combination of TAAR1 agonists with antipsychotics may be more efficacious ($N=2$, $SMD=0.90$, 95% CI: 0.00, 1.80) (extended data). Still, the effects were imprecise,

and there were insufficient data to explore potential sources of heterogeneity in these comparisons, which may also stem from different TAAR1 agonists and antipsychotics used.

The data for prepulse inhibition impairment, the second primary outcome, came from just one study in animal models of psychosis, so it was not analysed further.

Secondary outcomes

Secondary efficacy outcomes

There were limited data for secondary efficacy outcomes, with 4 studies reporting data for cognitive function^{55,56,63,69}. There were no clear differences between TAAR1 agonists and control ($N=4$, $k=5$, $SMD=0.80$, 95% CI: -0.30, 1.90) (extended data). Increasing the dose of TAAR1 agonists from levels reflecting

Table 2. Table of characteristics of non-human studies.

Study name	Year	Model	Strain and species	Interventions	Outcomes with usable data
Begni <i>et al.</i> 2021 ⁵⁵	2021	Pharmacological	Lister hooded (rat)	Ulotaront; Vehicle	Locomotor activity; Cognition
Cinque <i>et al.</i> 2018 ⁵⁶	2018	Genetic	Wistar (rat)	RO5203648; Vehicle	Cognition
Dedic <i>et al.</i> 2019 ⁵⁷	2019	Pharmacological	G57BL/6j (mouse); Sprague-Dawley (rat)	Ulotaront; Clozapine; Vehicle	Locomotor activity; Social interaction
Galley <i>et al.</i> 2012 ⁵⁸	2012	Pharmacological	Wistar (rat)	RO5073012; Vehicle	Locomotor activity
Kokkinou <i>et al.</i> 2021 ⁵⁹	2021	Pharmacological	C67BL/6 (mouse)	Ulotaront; Vehicle	F-DOPA PET
Krasavin <i>et al.</i> 2022a ⁶⁰	2022	Pharmacological; Genetic	Wistar (rat)	LK000764; Vehicle	Locomotor activity
Krasavin <i>et al.</i> 2022b ⁶¹	2022	Genetic	Wistar (rat)	AP163; Vehicle	Locomotor activity
Leo <i>et al.</i> 2018 ⁶²	2018	Genetic	Wistar (rat)	RO5203648; Vehicle	Locomotor activity
Liang <i>et al.</i> 2022 ⁶³	2022	Pharmacological	ICR (mouse)	Ulotaront; Ulotaront + Olanzapine; Olanzapine; Vehicle	Locomotor activity; Cognition
Revel <i>et al.</i> 2011 ⁶⁶	2011	Pharmacological; Genetic	C57BL/6j (mouse); NMRI (mouse)	RO5166017; Vehicle	Locomotor activity; Stereotypy
Revel <i>et al.</i> 2012a ⁶⁵	2012	Pharmacological; Genetic	C57BL/6jx129SvJ (mouse); C57BL/6j (mouse); Wister (rat)	RO5203648; Vehicle	Locomotor activity
Revel <i>et al.</i> 2012b ⁶⁴	2012	Pharmacological	C57BL/6j (mouse)	RO573012; Vehicle	Locomotor activity
Revel 2013 ⁶⁹	2013	Pharmacological	C57BL/6j (mouse); Long-Evans (rat); Not stated (mouse)	RO5256390; RO5263397; RO5256397 + risperidone; Olanzapine; Risperidone; Vehicle	Locomotor activity; Cognition
Saarinen <i>et al.</i> 2022 ⁶⁸	2022	Pharmacological	Not stated (mouse)	Ulotaront; Vehicle	Locomotor activity; Prepulse inhibition
Wang <i>et al.</i> 2023 ⁶⁷	2023	Pharmacological	C57BL/6j (mouse)	Compound 50A; Compound 50B; Aripiprazole; Risperidone; Vehicle	Locomotor activity

Vehicle: control condition in animal studies like placebo in clinical trials. A more detailed table of study characteristics with the included comparisons of interventions along with the sample size for each outcome can be found in the [extended data](#).

50% of the maximum efficacy to 80% might reduce efficacy, with the effect size decreasing on average by -0.21 (95% CI: -0.42, 0.00).

Dropouts

Dropouts were reported in 2.6% and 3.3% of animals allocated to TAAR1 agonists and control groups, respectively ([extended data](#)).

Adverse events

There were no usable data for adverse events in animal models of psychosis.

Mechanistic insights

TAAR1 agonists did not appear to have an effect compared to control on locomotor activity in animals subjected to both

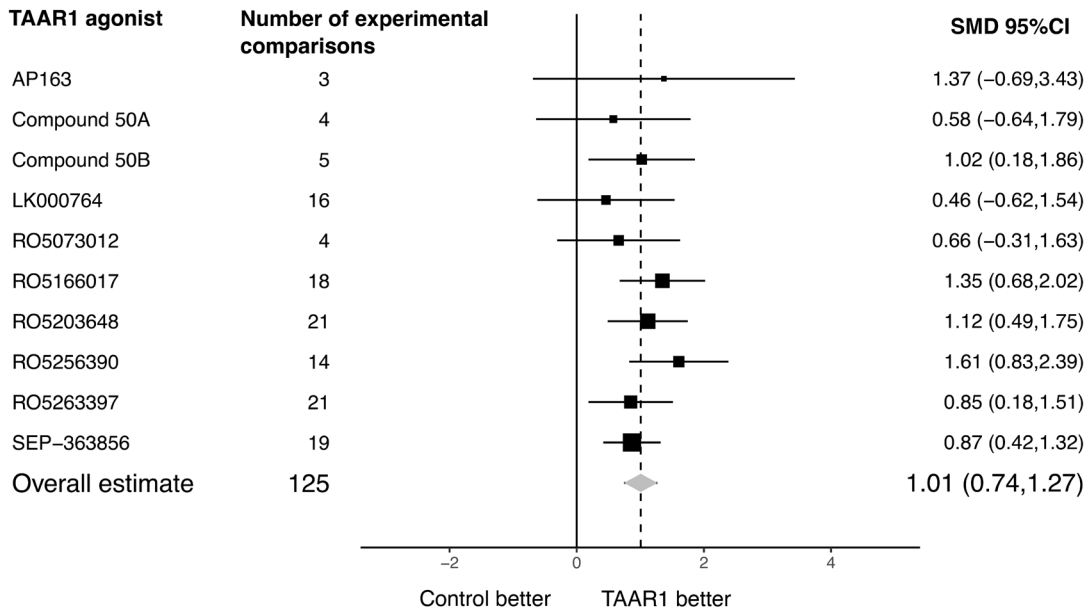
models of psychosis and TAAR1 knockout (N=2, SMD= -0.02, 95%CI: -1.15, 1.12) ([extended data](#)).

There were no usable data on neurobiological outcomes, except for some indications from one small study that ulotaront may decrease striatal dopamine synthesis capacity measured with F-DOPA PET compared to control in ketamine-treated mice when administered 2 days after completion of the ketamine treatment (SMD = -1.01, 95% CI: -2.04, 0.02)⁵⁹.

Discussion

For the first time, we combined a quantitative synthesis of data from human and non-human sources of evidence regarding the efficacy, tolerability, and mechanism of action of TAAR1 agonists in treating psychosis, which goes beyond previous reviews^{6,9,70-73}.

A. Subgroup analysis of TAAR1 agonists versus control on locomotor activity in animal models of psychosis by the specific compound administered



B. Meta-regression analysis of standardised dose of TAAR1 agonist versus control on locomotor activity in animal models of psychosis

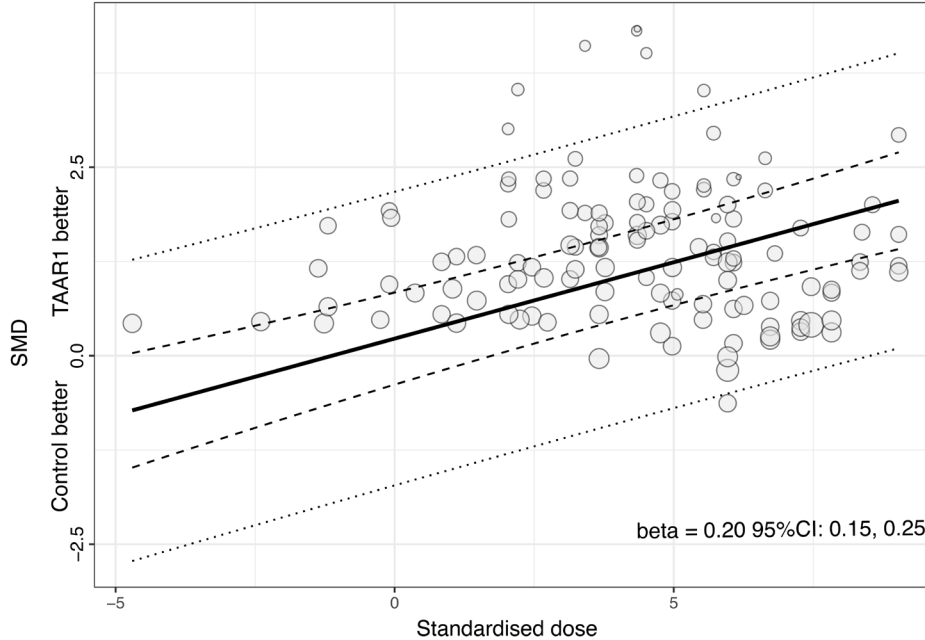


Figure 5. TAAR1 agonists versus control condition for locomotor activity in animal models of psychosis. A. Subgroup analysis of TAAR1 agonists versus control condition (e.g., vehicle) for locomotor activity in animal models of psychosis by the specific compound administered. The forest plot presents the overall estimate and the pooled estimates for each of the 10 different TAAR1 agonists by combining data from experimental comparisons. SEP-363856 refers to ulotaront. **B.** Meta-regression analysis of standardized dose of TAAR1 agonists versus control on locomotor activity in animal models of psychosis. A standardised dose was calculated by taking into consideration the drug potency to TAAR1 receptor, with a standardised dose of 0 reflecting 50% and of 1 around 80% of the maximum effect, respectively (see [extended data](#)). The dashed lines represent the 95% confidence intervals, and the dotted lines the 95% prediction intervals. The beta for the slope is also presented indicating the change in the magnitude of the effect size per unit change in standardised dose. SMD: Standardized mean difference; 95%CI: 95% confidence intervals.

Forest plot of TAAR1 agonists versus antipsychotic drugs on locomotor activity in animal models of psychosis

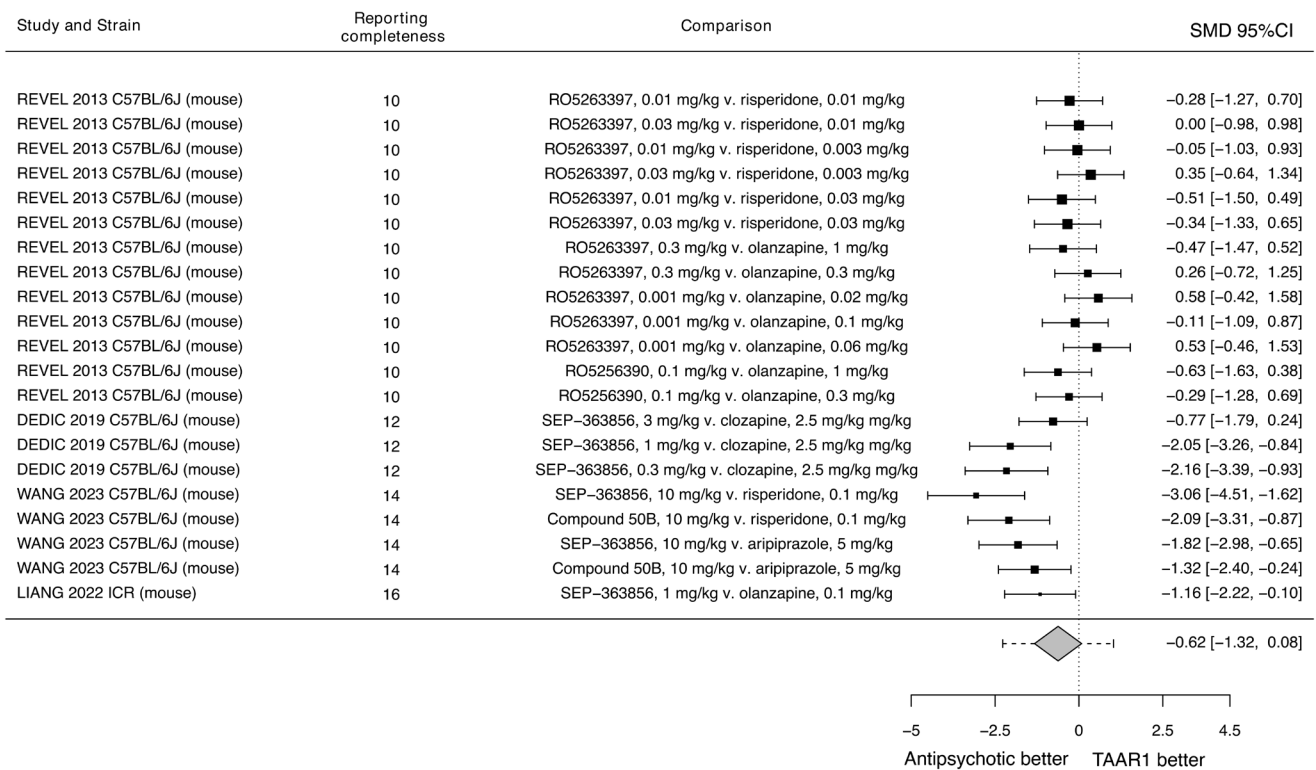


Figure 6. TAAR1 agonists versus already licensed antipsychotics for locomotor activity in animal models of psychosis. Forest plot of TAAR1 agonists versus antipsychotic drugs already licensed for schizophrenia on locomotor activity in animal models of psychosis. The effect sizes for each experimental comparison and the pooled estimate from the multilevel meta-analysis are presented. The dotted lines around the pooled estimate represent the 95% prediction intervals. The reporting completeness according to the modified ARRIVE checklist is also presented. SEP-363856 refers to ulotaront. SMD: Standardised mean difference, 95%CI: 95% confidence interval.

Summary of findings and interpretation

TAAR1 agonists may be less efficacious than dopamine D_2 receptor blocking drugs licensed for schizophrenia, yet the results are inconclusive. In clinical trials, ulotaront and ralmataront exhibited an average effect size of 0.15 compared to placebo in acute schizophrenia, which is smaller than other antipsychotics (ranging from 0.24 to 0.89)¹. However, large placebo responses in the two ulotaront phase III trials raised assay sensitivity concerns^{50,51,54}. This could be partly attributed to recruitment challenges during the COVID-19 pandemic, and a post-hoc analysis using participants recruited before the pandemic reported efficacy comparable to that of the phase II trial (Figure 2)^{7,54}. Limited data were available for direct comparisons between the two drug classes, with ralmataront being less efficacious than risperidone in one trial⁵². Additional insights were provided by animal studies that examined more compounds and revealed that TAAR1 agonists may be less efficacious when directly compared to dopamine D_2 receptor blocking antipsychotics. Still, TAAR1 agonists demonstrated dose-dependent positive effects compared to control groups in these studies. This may suggest that the doses

in human studies might have been insufficient (up to ulotaront 100mg/d, ralmataront 150mg/d). Nevertheless, no dose-response relationship was identified for ulotaront up to 10mg/kg/day in rodents, roughly corresponding to 75–150mg/day in humans⁷⁴.

In terms of tolerability, evidence from clinical trials suggested that TAAR1 agonists may have a relatively benign side-effect profile, as ulotaront and ralmataront did not show clear differences from placebo in adverse events over 4–6 weeks. However, single-dose trials of ulotaront reported sedation and nausea/vomiting, indicating possible transient effects.

From a mechanistic standpoint, limited but consistent evidence from F-DOPA PET human and animal studies suggested that ulotaront may alleviate presynaptic dopamine dysregulation in the striatum^{53,59}, a central factor in the development of psychosis symptoms⁷⁵, in contrast to dopamine D_2 receptor blocking drugs^{76,77}. Additionally, the findings from animal models of psychosis indicated that TAAR1 agonists potentially exert their beneficial effects through TAAR1-dependent interference with dopaminergic signalling. However, sedative effects

may also play a role potentially explaining the opposite direction of the dose-response relationships for locomotor activity and cognitive function.

Limitations

The review had some limitations. First, data were available for a limited number of TAAR1 agonists, and only ulotaront and ralmataront in human studies, which may not be generalisable for this entire drug category. Recent studies have shed further light on the structure and function of TAAR1, paving the way on developing new drugs with unique pharmacological properties, such as functional selectivity, that may yield different findings^{10,11,78–81}. Additionally, clinical trials were primarily conducted in the United States of America and Eastern Europe with limited representation of countries from the global south.

Second, there was missing evidence. We could not include all data from unpublished human studies, including those involving adolescents⁵⁰, predominant negative symptoms (terminated early due to inefficacy in interim analysis)⁸², the maintenance phase⁸³, and from the ulotaront phase III trials^{50,51} for which we could only locate data on overall symptoms from a conference abstract⁵⁴. Additionally, there was the possibility that relevant animal studies were unpublished or missed, as indicated by small-study effects. Although we comprehensively searched multiple databases, conventional screening of titles/abstracts underperform in identifying non-human studies⁸⁴. Thus, alongside conducting the first iteration of this review, we developed systematic online living evidence summaries (SOLES)⁸⁴ for preclinical psychosis research (**Psychosis-SOLES**)⁸⁵ that use automated tools to facilitate study identification. To further improve future review updates, we used the current search terms and data extraction template for human data as input to the development of associated ontology classes and relationships⁸⁶, which would support data searching and data-driven algorithms for enrichment and inference.

Third, we focused on RCTs and excluded uncontrolled and observational human studies. Uncontrolled studies mainly addressed pharmacokinetics (see excluded studies in [extended data](#)), except for the six-month open-label extension of the ulotaront phase II trial⁷, which highlighted its long-term efficacy and benign side-effect profile⁸⁷. Observational studies, including genetic and post-mortem studies, have suggested an association between dysregulated TAAR1 activity and schizophrenia^{6,88–90}. In non-human studies, we focused on *in vivo* animal models of psychosis and excluded those not subjected to such models. However, TAAR1 agonists can still be evaluated in naïve animals or other specific models^{10,57,91}. For example, ulotaront appeared to have a similar efficacy in improving prepulse inhibition (co-primary outcome in the synthesis of non-human data) in both naïve animals⁵⁷ and models of psychosis⁶⁸. Yet, meta-analysis for this outcome was not feasible in this review iteration due to limited data from only one study using animal models of psychosis⁶⁸. We

excluded *in vitro* studies despite insights they could offer on the mechanism of action of TAAR1 agonists⁶. Synthesizing their data would be challenging due to the limited established systematic review methods^{92,93}.

Finally, we were unable to explore heterogeneity due to the small number of human studies. Individual participant data are necessary for refined examination of potential participant-level characteristics, including age, sex, chronicity of illness, baseline severity, and understanding potential reasons for the small effect sizes observed in ulotaront phase III trials^{50,51}. Moreover, differences in the findings of human and non-human studies underscored the challenges of modelling a complex and subjective condition like psychosis in animals, with unclear and limited validity^{4,94,95}. This emphasises the need for systematic examination and improvement of the translatability of animal models of psychosis.

Reflections on the co-production of the review

GALENOS experiential advisors^{12,13}, co-produced the plain language summary, contributed to protocol design and interpretation of the findings. They also improved the presentation of review methodologies and findings to the wider public. Emphasis was placed on contextualising the effects of new medications with those of already licensed antipsychotics, especially regarding symptoms of psychosis, such as hallucinations and delusions, and adverse events like weight gain.

This review is the first of a series of living systematic reviews within the GALENOS project¹², establishing the basis for inclusion of experiential advisors in future reviews and development of a more systemic co-production process. Honest discussions addressed the nature of engagement of experiential advisors in academic setting (e.g. working towards deadlines, in large teams across multiple countries), the need for responsive two-way communication, and the challenges faced. The aim was for experiential advisors to be involved as equal partners in review teams, underscoring the importance of training and supporting experiential advisors and researchers, and of levelling the field so that participants understand well enough the content of the work being carried out. Consequently, alongside with conducting the review, we co-produced guidance on how best to include experiential advisors in the GALENOS reviews¹⁴.

Conclusions

Evidence from both human and animal studies suggested that current TAAR1 agonists may offer smaller benefits in improving symptoms of psychosis compared to dopamine D₂ receptor blocking drugs already licensed for schizophrenia. However, the findings were inconclusive due to possible biases, and there was some disconnect between human and animal studies, highlighting the need for further improving the translatability of animal models in the context of psychosis. Limited evidence also suggested that TAAR1 agonists may

regulate presynaptic dopaminergic signalling and have a relatively benign side-effect profile. The field of TAAR1 research remains active, with ongoing drug development. Thus, the TAAR1 mechanism of action still holds promise for the treatment of psychosis, with emerging evidence expected in the near future. Future iterations of this living systematic review and meta-analysis will aim to incorporate these new developments.

Ethics and consent

Ethical approval and consent were not required.

Abbreviations

5-HT_{1A}: Serotonin 5-HT_{1A} receptor; 95%CI: 95% confidence intervals; ARRIVE: Animal Research Reporting of *In Vivo* Experiments; d: Day; D₂: Dopamine D₂ receptor; EPPI-Reviewer: Evidence for Policy, and Practice Information and Coordinating Centre - Reviewer; F-DOPA: Fluorodopa; GALENOS: Global Alliance for Living Evidence on Anxiety, Depression, and Psychosis; GRIPP: Guidance for Reporting Involvement of Patients and the Public; k: Number of experiments; kg: Kilogram; mg: Milligram; N: Number of studies; n: Number of participants; NMD: Normalised mean differences; OR: Odds Ratio; PANSS: Positive and Negative Syndrome Scale; PET: Positron emission tomography; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA-S: PRISMA Statement for Reporting Literature Searches; RCT: Randomised controlled trials; RoB2: Risk of Bias 2 tool; SEP-363856: Ulotaront; SMD: Standardised mean differences; SyRF: Systematic Review Facility; TAAR1: Trace amine-associated receptor 1

Data and software availability

Underlying data

The data for this article consists of bibliographic references, which are included in the References section.

Aggregated data and R code for the analysis can be found in the GitHub repositories for the project:

- Human studies: https://github.com/galenos-project/LSR3_taar1_H. The archived aggregated data and analysis code

at time of publication, <https://doi.org/10.5281/zenodo.10890206>⁴³

- Non-human studies: https://github.com/galenos-project/LSR3_taar1_A. The archived aggregated data and analysis code at time of publication, <https://doi.org/10.5281/zenodo.10890218>⁴⁴.

Underlying data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

Extended data

Open Science Framework: Trace amine-associated receptor 1 (TAAR1) agonists for psychosis: protocol for a living systematic review and meta-analysis of human and non-human studies, <https://doi.org/10.17605/OSF.IO/TDMAU>⁹⁶.

This project contains the following extended data:

- The report of the findings for the human studies published in Rpubs: https://rpubs.com/sksiafis/LSR3_TAAR1_H
- The report of the findings for the non-human studies published in Rpubs: https://rpubs.com/VirginiaChiocchia/LSR3_TAAR1_A

Extended data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

Reporting guidelines

Open Science Framework: PRISMA 2020, PRISMA-S and GRIPP2 checklists can be found in Open Science Framework, <https://doi.org/10.17605/OSF.IO/TDMAU>⁹⁶.

Completed checklists for the corresponding reporting guidelines are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Gavin P Reynolds 

Sheffield Hallam University, Sheffield, England, UK

This article addresses the role of TAAR1 agonist/partial agonist drugs in the treatment of psychosis. It has a rigorous approach and is co-produced with "experiential advisors"; I also believe it is unique in its approach of synthesising data from both human and non-human studies. In the light of recent clinical reports, its findings are perhaps unsurprising - that TAAR1 agonists have a "relatively benign" profile in terms of adverse effects but may be less effective than current antipsychotic treatments.

Previous reviewers have made some suggestions/comments but there are no comments from the authors or indication of how the review may have been modified in response. There have been some modifications "post hoc" including a focus on RCTs rather than including all experimental human studies; this deserves emphasising more clearly when ref 18 is mentioned, rather than just referring to "extended data". The protocol provides a useful list of research questions; it would have been valuable to have those repeated here.

Most definitely the living review format is a valuable one in this rapidly moving field, although on current clinical evidence its lifetime may be limited!

Given the statements in recent publications suggesting a possible efficacy of ulotaront on negative symptoms, it would have been valuable to have seen this addressed explicitly in the clinical and animal data, if only to say there is inadequate/inconsistent evidence.

Notwithstanding the involvement of the experiential advisors, there is some excessive use of jargon - one example being that of "triangulation" which means different things to different people; a few words of explanation as to what is considered in a triangulation meeting would be helpful.

While the assessment of dropouts is important in clinical studies, the use of this term in the animal studies is confusing since it inevitably relates to technical issues rather than factors such as tolerability.

It would have been valuable to have included in the animal forest plots a word indicating the psychosis model used for each of the studies.

The authors provide a useful limitations section.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Psychopharmacology and biological psychiatry of schizophrenia

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 17 July 2024

<https://doi.org/10.21956/wellcomeopenres.23562.r80883>

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Pramod Nair 

Flinders University, Adelaide, South Australia, Australia

The manuscript by Siafis *et al.*, provides a comprehensive systematic review and meta-analysis of human and non-human data on trace amine-associated receptor 1 (TAAR1) agonism for psychosis. This is an important 'living' systematic review examining the effects of TAAR1, which aims to provide regular updates on this emerging pharmacological target in the field of psychosis and neuropsychiatric disorders.

The current study includes 9 clinical RCT studies, investigating the effects of TAAR1 agonists on a total of 1683 individuals (average age: 32.9 years, 69.8% men, 30.2% women), and 15 preclinical studies conducted on different laboratory psychotic mice models.

According to this study, TAAR1 agonists may be less effective than dopamine D2 receptor antagonists already available for treating schizophrenia. However, this interpretation is considered preliminary and inconclusive due to the limited number of drugs examined, the lack of longer-term data, the disconnect between human and animal studies, publication bias, etc. There is also limited evidence that suggests TAAR1 agonists may promote presynaptic dopaminergic signalling while being relatively safe. Overall, the authors provided a widespread overview and effectively described the current state of TAAR1 agonists for the treatment of psychosis. Considering the ongoing development of TAAR1 agonists and their potential to treat neuropsychiatric disorders, the article and any future iterations carry a great deal of importance.

Minor errors need to be addressed:

Figure 1:

The screening section mentions n=165 studies. Under the section "Findings from human studies" on page 12, Study description, Line 1 shows 166 full texts. Which one is true?

Page 13: Primary outcome:

Lines 3-4 say participants n= 1291. In table 1, total sample size of all 4 studies is 1457. Not clear. Line 14 says participants N = 156. This number doesn't match the numbers in Figure 2A or Table 1. If exclusions are made it needs to be mentioned in the text/legends.

In Table 1:

According to clinicaltrials.gov, NCT04092686 (<https://clinicaltrials.gov/study/NCT04092686>) had 464 (actual enrolments), 462 (subjects). Same with NCT04072354 (<https://clinicaltrials.gov/study/NCT04072354?cond=NCT04072354&rank=1>), 463 (actual enrolment), 435 subjects. Which numbers are considered? Actual enrolment or treatment subjects? The same extends to all other studies mentioned here.

The primary outcome, Second paragraph: "... Ralmitaront was less efficacious than the antipsychotic". Which figure is showing this?

Figure 2B: units on the x-axis show "mg//d" Is it meant to be mg/d?

Figure 3:

A legend is required for the colours, what do green circles represent? What is red? The figure needs refining. Can the grey cross lines be removed? The labels need to be aligned properly. For example: see the "dropouts" section, the line is sitting on top of the text. Keep consistent font size and colours. Some dots seem to be bigger than others. What does it mean? Should be clarified in the legends.

Figure 5:

Standardised dosage. Units?
Some squares seem to be bigger than others. What does it mean?

Suggestion: All figures comparing “placebo/antipsychotic better or TAAR1 better”, will be easier for the reader if they are colour-coded. Red when placebo/antipsychotic is better and green when TAAR1 is better or vice versa. Removing the minor and major gridlines from all figures may help present cleaner figures.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the ‘living’ method appropriate and is the search schedule clearly defined and justified? (‘Living Systematic Review’ or a variation of this term should be included in the title.)

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Schizophrenia pharmacology, neuropsychiatric disorders, drug design and discovery, development of small molecular therapeutics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 20 June 2024

<https://doi.org/10.21956/wellcomeopenres.23562.r85389>

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Keiko Ikemoto 

The University of Tokyo, Tokyo, Japan

The authors try to review efficacy of TAAR1 for psychosis combined with meta-analysis of human and non-human data. In humans, data of clinical trials of ulotaront and ralmitaront were available, which showed mild effectiveness of TAAR1 agonists for treatment of psychosis.

The authors mention placebo effects, possible influence of COVID-19 pandemic on results of clinical trials, and expectancy of TAAR1 agonists.
This is a timely review.

Previous post-mortem brain studies by Ikemoto et al (Ref -1). have shown the reduction of TAAR1-ligand neurons (D-neurons) in the nucleus accumbens, an antipsychotic acting site, of patients with schizophrenia (with long disease duration), which is a backgrounded datum for expectancy of TAAR1 medicinal chemistry. Please cite this study and discuss the results based on the post-mortem brain study.

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: clinical psychiatry, histochemistry

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
