Efficacy and safety of flupentixol-melitracen in patients with refractory chronic cough: a randomised, double-blinded, placebo-controlled clinical trial

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Summary

Background The antitussive potential of flupentixol-melitracen, an anti-anxiety and anti-depression compound, has been observed previously. We aimed to further evaluate its efficacy and safety in patients with refractory chronic cough (RCC) who were unresponsive to any other available treatments.

Methods This randomised, double-blinded, placebo-controlled clinical trial was conducted at a single specialist cough clinic in Tongji Hspital, Shanghai, China. Adults aged 18–69 years with RCC and persistent cough despite at least two weeks of neuromodulator therapy were enrolled. Participants were randomly assigned (1:1) to receive either oral flupentixol-melitracen (flupentixol 0.5 mg + melitracen 10 mg), one tablet twice daily, or matching placebo, for two weeks, followed by a one week of off-treatment safety monitoring. Randomisation was computer-generated, with masking of participants, investigators, and outcome assessors. The co-primary endpoints were cough resolution rate (≥50% reduction in cough symptom score [CSS]) at visit four and placebo-adjusted change in CSS over time. The full analysis set (FAS) was used following the modified intention-to-treat (mITT) principle for demographic baseline analysis and efficacy analysis. The safety set (SS) was used for safety analysis and included all patients who took at least one dose of treatment and had post-dose safety records. The FAS and SS were equivalent in this study. The trial is registered with the Chinese Clinical Trial Registry, ChiCTR2000035304.

Findings Between March 9th, 2021 and December 1st, 2023, 102 patients were enrolled and randomised. A total of 99 patients received at least one dose of treatment and were included in the primary and safety analyses (49 taking flupentixol-melitracen and 50 taking placebo). At visit four, flupentixol-melitracen arm reached significantly higher cough resolution rate (65.3% [32/49] vs 32.0% [16/50]; p = 0.0009). The adjusted mean reduction in CSS was 0.144 points greater in the flupentixol-melitracen group than in the placebo group over time (p = 0.0034). Treatment-emergent adverse events occurred in 51.0% (15/49) of patients in the flupentixol-melitracen group and 34.0% (17/50) in the placebo group. No serious adverse events or treatment-related deaths were reported. All adverse events were mild and resolved after discontinuation.

Interpretation Our findings suggest that short-term use of flupentixol-melitracen may be an effective and well-tolerated treatment for RCC. However, the findings should be interpreted with caution due to key limitations, including the absence of objective cough frequency measurement and limited generalisability beyond a single-centre population. These factors may influence the precision and applicability of the observed treatment effect. Further trials using objective endpoints and longer follow-up in broader populations are needed to confirm efficacy and safety.

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Research in context

Evidence before this study

We systematically searched PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to February 28, 2021, without language restrictions, using the search terms: ("flupentixol" OR "melitracen" OR "Deanxit") AND ("chronic cough" OR "refractory cough" OR "antitussive"). Reference lists of relevant publications and international clinical guidelines on chronic cough were also reviewed. We included clinical trials and observational studies investigating the use of flupentixol-melitracen in adults with chronic cough, and excluded studies that focused exclusively on psychiatric outcomes without cough-related endpoints. This search identified no randomised controlled trials and no pooled analyses assessing the antitussive efficacy of flupentixol-melitracen. The present trial was designed on the basis of preliminary clinical observations from our own cohort study, which subsequently demonstrated symptomatic improvement and reduced capsaicin cough sensitivity in patients with refractory chronic cough. These findings were published in August 2021. However, the observational study was limited by its non-randomised design, lack of a comparator group, and susceptibility to selection and placebo response. At the time of trial design, robust clinical evidence supporting the antitussive effect of flupentixol-melitracen was therefore lacking.

Added value of this study

To our knowledge, this is the first randomized, double-blinded, placebo-controlled study to provide robust evidence for the antitussive potential of flupentixol-melitracen in patients with refractory chronic cough who were unresponsive to neuromodulators. This study may provide evidence for an additional treatment option for cough patients.

Implications of all the available evidence

Findings from this trial suggest that short-term treatment with flupentixol-melitracen may offer a therapeutic benefit for patients with refractory chronic cough who are unresponsive to existing therapies. However, several limitations—namely the absence of objective cough frequency assessment, the potential for unblinding due to treatment-emergent adverse events, and the single-centre study design—may constrain the interpretation and external validity of the results. These factors highlight the need for further confirmatory studies incorporating objective outcome measures, extended follow-up periods, and broader patient populations across multiple centres to fully establish the clinical utility, safety, and optimal regimen of flupentixol-melitracen in this context.

Introduction

Chronic cough (CC), defined as a cough lasting more than eight weeks, affects approximately 10% of the global population, leading them to seek medical care. With updated international and national guidelines,[1,2] the diagnosis and management of CC have become more standardised, allowing the identification and treatment of the underlying causes in most patients. However, 5%–42% of patients either do not respond to targeted treatments or the causes remain unclear.[3] These patients are commonly referred to as having refractory chronic cough (RCC), a term frequently used in clinical trials.

Increasing evidence has indicated that dysregulation of neural pathways is the fundamental mechanism of CC,[4] which brings rationale for introducing neuromodulators such as baclofen, gabapentin, and pregabalin in the treatment of RCC.[5,6] However, these medications are effective in only two-thirds of patients in real-world clinics and are associated with well-known adverse reactions such as sedation.[7] A massive placebo response has been commonly reported in cough trials.[8] To date, there is no solid evidence to show such treatments do not act as placebos, since only gabapentin has been studied in a well-designed placebo-controlled randomised clinical trial, however with a small sample size.[9]

Flupentixol-melitracen (trade name: Deanxit; H. Lundbeck A/S, Denmark) is a compound medication consisting of an antipsychotic (0.5 mg of flupentixol) and a tricyclic antidepressant (10 mg of melitracen). It is marketed and commonly prescribed for mild to moderate depression and anxiety in China and several other countries.[10] In our previous clinical observation, flupentixol-melitracen (one tablet, twice daily) was found to effectively improve cough symptoms and cough-specific quality of life (QoL) in 62.4% (63/101) of patients with RCC, along with a reduction in peripheral

cough sensitivity to capsaicin.[11] However, given the inherent limitations of an observational study design, these findings were suggestive rather than conclusive. Based on these preliminary observations, we hypothesised that flupentixol-melitracen may exert an antitussive effect in patients with RCC who lack effective treatment options. Therefore, the present double-blinded, randomised, placebo-controlled clinical trial (RCT) was designed to rigorously evaluate the benefits and risks of oral flupentixol-melitracen 10.5 mg taken twice daily in patients with RCC unresponsive to other available treatments.

Methods

Study design

This randomised, double-blinded, placebo-controlled clinical trial recruited participants from the specialist cough clinic at Tongji Hospital between March 9th, 2021 and December 1st, 2023. The trial consisted of a run-in period (day −7∼0), a treatment period (day 1∼14), and a follow-up period (day 15∼21) (Supplementary Figure S1). The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines. The protocol was approved by the ethics committee in Tongji Hospital (Approval No. 2021-007) and registered in Chinese Clinical Trial Registry (Registry No. ChiCTR2000035304). The study adheres to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines for the reporting of randomised controlled trials.

Participants

The diagnosis of RCC was made by the primary investigator when no treatable traits, such as asthma, reflux, or rhinosinusitis, were identified in accordance with the latest Chinese cough guideline.[2] Male and female patients with RCC aged ≥18 but <70 years, who scored at least three points on the total cough symptom score (CSS)[12] and had failed to respond to at least two weeks treatment of gabapentin (900 mg daily), baclofen (60 mg daily), or pregabalin (450 mg daily), were included in the study. Exclusion Criteria included: 1) current smokers or ex-smokers who quit less than two years ago; 2) recent upper airway infection in the past eight weeks; 3) a history of allergy or contraindications to flupentixol-melitracen or any ingredients of placebo; 4) women who were pregnant or breastfeeding; and 5) active liver and kidney disease. Use of other antitussive medications was not allowed. All participants provided written informed consent.

Randomisation and masking

Eligible participants with RCC were randomly assigned to receive encapsulated flupentixol-melitracen (Manufacturer: H. Lundbeck A/S, Denmark, Product Batch Number: 2665567 0210125, brand name Deanxit) or matching placebo (manufactured by Hunan Kangzhe Pharmaceutical Co., Ltd., provided by H. Lundbeck A/S, China agent) in a 1:1 ratio. Participants and trained research trial staff who had direct contact with the patients were blinded to the assigned treatment. Flupentixol-melitracen and placebo were visually identical to maintain masking for both participants and trial staff. Randomization was achieved through computer-generated random numbers, which were used to create the allocation table that facilitated the balanced distribution of patients across the two treatment groups. Independent personnel, who were not blinded to the treatment allocation, were responsible for the preparation of the study medication in sequentially labeled containers following the randomization list. The random allocation scheme was securely stored in opaque, double-sealed envelopes and retained by the assigned personnel. The enrolled patients received their trial tablets from these labelled containers, which were sequentially dispensed by trial staff. This process was regularly audited by an independent monitor to ensure strict adherence to the protocol. For each study treatment, a detailed documentation log was kept. The trial staff registered patients information with an online electronic form and they remained blinded to the allocation sequence. Data collection and analysis were also conducted in a masking manner. Blinded study personnel evaluated the safety and effect outcomes and completed the assessment before the final unblinding. To ensure accurate masking, the trial staffs and patients had to declare which study treatment they believed was provided.

Procedures

Participants received flupentixol-melitracen tablet 10.5 mg or matching placebo twice daily in the morning and lunchtime for two weeks, followed by one week of off-treatment safety follow-up.

Cough condition and QoL were assessed using patients' self-reported outcomes (PROs) including the CSS,[12] cough severity Visual Analogue Scale (VAS),[13] Hull Airway Reflux Questionnaire (HARQ) score,[14] Leicester Cough Questionnaire (LCQ),[15] Newcastle Laryngeal Hypersensitivity Questionnaire (NLHQ),[16] and capsaicin cough challenge test (recorded as the minimum concentrations of capsaicin required to stimulate two coughs [C2] and five coughs [C5]),[17] at appropriate visits. The CSS, introduced by Hsu et al. in 1994 is a concise and user-friendly instrument designed to assess subjective cough frequency during both daytime and nighttime periods.[12] Each component is rated on a scale from 0 to 5, with a cumulative score ranging from 0 (indicating no cough) to 10 (representing the most severe cough). Due to its brevity and ease of use, the CSS has been extensively adopted in both research and clinical settings.[18] Studies have demonstrated that

95% of patients who perceived improvement in their cough symptoms reported a decrease of one to three points in their total CSS[19] with an effect size of one point.[20]

The presence of anxiety and depression was also evaluated in this trial, using the Generalised Anxiety Disorder-7 (GAD-7),[21] Hamilton Anxiety Rating Scale (HAM-A),[22] Patient Health Questionnaire-9 (PHQ-9),[23] and Hamilton Depression Rating Scale-24 (HAMD-24).[24]

The preliminary efficacy of the trial intervention (flupentixol-melitracen vs placebo) was evaluated based on patient-reported outcomes collected at: (T0; vist 0) screening, prior to enrollment and before randomization; (T1; visit 1) baseline, following randomization and before the intervention; (T2; visit 2) 1-week, (T3; visit 3) 2-weeks, and (T4; visit 4) 3-weeks post-intervention. Data were collected either in person or via telephone or through WeChat, ensuring the assessment's comprehensiveness and reliability. (Supplementary Table S1).

Outcomes

The co-primary endpoints were cough resolution rate[25–27] (defined as percentage of patients with a total CSS decrease of at least 50% from baseline) including control rate (defined as percentage of patients whose cough entirely disappeared) and responsive rate (defined as percentage of patients with a total CSS decreased of $\geq$50% but <100%) of flupentixol-melitracen compared to placebo at T4 and placebo-adjusted change in CSS over time.

Key secondary endpoints included changes in VAS, HARQ, and LCQ over time compared to placebo. Other secondary endpoints were changes in NLHQ, GAD-7, HAM-A, PHQ-9, and HAMD-24 over time compared to placebo.

Safety assessment included the incidence of any treatment-emergent adverse events (TEAEs) assessed up to week three.

Statistical analysis

The sample size was calculated using PASS software (Power Analysis and Sample Size Software [2020]. NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass). Based on our previous observational study,[11] the efficient rate of flupentixol-melitracen for patients with RCC was 63%. Assuming the placebo response would be 30% (the median reported in various clinical trials[8]), a sample size of 43 patients per group yields 90% power at a one-sided significance level of 0.025 with a two-sample test for the primary endpoint. Adjusting for approximately 15% dropout rate results in a target sample size of 51 patients per group and a total sample size of 102 patients. The choice of a one-sided significance level of 0.025 was based on our directional hypothesis that flupentixol-melitracen would demonstrate superior efficacy compared to placebo in treating RCC. One-sided tests are appropriate when the research hypothesis predicts a specific direction of effect, thereby increasing the test's power to detect a difference in that direction. This approach aligns with standard statistical practices, where a one-sided test at an alpha level of 0.025 corresponds to a two-sided test at the conventional 0.05 level, maintaining the overall type I error rate.

The full analysis set (FAS) was used following the modified intention-to-treat (mITT) principle for demographic baseline analysis and efficacy analysis. The safety set (SS) was used for safety analysis and included all patients who took at least one dose of treatment and had post-dose safety records. The FAS and SS were equivalent in this study.

Statistical analyses were performed using IBM SPSS Statistics (Version 29.0), R Statistical Software (v4.4.1; R Core Team 2021) and Python (version 3.11.4, Python Software Foundation, Wilmington, DE). Normality was assessed with the Kolmogorov–Smirnov test. The normally distributed data were expressed as mean (standard deviation [SD]) and skewed distributed data were expressed as median with IQR. C2 and C5 were log-transformed and shown as geometric mean. The proportion of missing data for the predictor variables ranged from 1.0% (1/99) for age to 17.2% (17/99) for HARQ. Overall, 25.3% (25/99) of the participants had missing values for at least one predictor variable. To address this issue, multiple imputation using chained equations was performed under the assumption that data were missing at random. This approach was selected over complete case analysis, which risks loss of statistical power and potential selection bias, and single imputation, which may underestimate variance. Multiple imputation enhances statistical efficiency and stability by generating multiple plausible datasets, particularly when complex relationships among predictors exist, and is superior to alternative methods such as inverse probability weighting. We generated 20 imputed datasets, pooled results using Rubin's rules, and retained all 99 participants to maximize statistical power and ensure unbiased estimates. The fully imputed dataset was used for the outcome analyses, while a complete case dataset, which included only participants without missing values for any predictor variables, was employed for subsequent sensitivity analysis.[28]

Continuous primary outcomes (Daytime CSS and nighttime CSS) and secondary endpoint (VAS, HARQ, LCQ, NLHQ, GAD-7, HAM-A, PHQ-9, and HAMD-24) across T1, T2, T3, T4 were examined using generalised linear mixed models (GLMMs) for repeated measures analysis. Analyses were adjusted for age and gender as covariates. The linearity assumption for the continuous predictors within the models was assessed using quadratic terms. Three 'Time' variables (reflecting a

piecewise approach for T1-T2, T2-T3, T3-T4), Condition (flupentixol-melitracen vs placebo), and corresponding Time × Condition interactions were specified as fixed effects, and a random intercept for participants was included. A skewed random error distribution with Wald Z statistic and a probit link function was employed. Effect sizes were calculated based on relevant modelled median differences and IQR at the relevant timepoints. Random effects are assumed to follow a non-normal distribution. The sequential Bonferroni correction (Holm-Bonferroni) was used to adjust for multiple testing among T1, T2, T3, T4 timepoints with an overall significance level of 0.05. The p-values of these comparisons were ordered from smallest to largest (P1 to Pk). The first p-value (P1) was compared to α/k, the second (P2) to α/(k-1), and so on, until a p-value was no longer significant. All subsequent p-values were considered non-significant. Cough resolution rate at T4 was evaluated using logistic regression. The odds ratios (ORs) along with their 95% confidence intervals (CIs) and p-values were derived from the model parameter estimates. Pre-defined subgroups analyses for primary endpoint were conducted between trial arms using chi-square tests. Crude risk ratios (RR) along with 95% CIs were calculated from 2 × 2 contingency tables. For subgroups with zero cells in one arm, a continuity correction was applied before calculating the unadjusted RR and their CIs. Specifically, 0.5 was added to all cells of the contingency table for that particular comparison. All pre-specified covariates were incorporated as adjustment factors in the analytical framework, including sex, age, cough duration, baseline cough condition, and metal health condition. Therapeutic response rate and incidence of TEAEs were assessed using the chi-squared test. Fisher's exact test was applied to contingency tables with no expected cell count less than 1 or at most 20% of expected cell counts less than 5. To minimise sparse data bias, the adjusted RR for per-person reported adverse events between the treatment groups was calculated with a 95% CI using robust variance estimation from modified Poisson regression.[29] A p-value <0.05 was considered statistically significant.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. ALL authors had full access to the data in the study. ZQ and KL had final responsibility for the decision to submit for publication.

Results

Baseline characteristics

Of the 108 patients with RCC screened, six were deemed ineligible. Ultimately, 102 patients were enrolled and randomised, with 51 assigned to receive flupentixol-melitracen and 51 assigned to receive a placebo. Of these, 99 patients (49 in the flupentixol-melitracen arm and 50 in the placebo arm) received at least one dose of the investigational drug and were included in both the FAS and SS. In the subset of 51 patients in the flupentixol-melitracen arm, 48 (94.1%) completed the two-week treatment, and 49 attended the visit four off-drug safety follow up at the end of week 3. In the placebo arm, 46 patients completed the two-week treatment and attended the visit four. Reasons for dropout and drug discontinuation are detailed in Fig. 1.

The demographic and clinical characteristics of the study participants included in the FAS were balanced at screening or baseline. The mean age of participants in flupentixol-melitracen arm and placebo arm was 49.0 (SD: 15.7) years and 52.5 (SD: 14.7) years, respectively. Both groups included 29 female patients, with a cough duration of 24.0 (IQR: 12.0–72.0) months and 32.0 (IQR: 9.5–72.0) months in flupentixol-melitracen arm and placebo arm, respectively. Most patients had dry coughs and coughed during the day. Other clinical characteristics are summarised in Table 1.

Primary efficacy endpoints

In the FAS, 18.4% of patients (9/49) receiving flupentixol-melitracen and 8.0% of patients (4/50) receiving placebo achieved cough control at visit four (OR and 95% CI: 2.59 [0.74–9.05]; p = 0.14). Response was reported in 46.9% of patients (23/49) taking flupentixol-melitracen and 24.0% patients (12/50) taking placebo (OR and 95% CI: 2.80 [1.19–6.61]; p = 0.019). The overall cough resolution rate was significantly higher in flupentixol-melitracen arm compared to the placebo arm (65.3% [32/49] vs 32.0% [16/50]; p = 0.0009) (Fig. 2a).

The GLMM model-based estimates and Time × Condition interaction effects for primary endpoints are presented in Table 2. There were significant differences in the over-time changes of daytime CSS (p = 0.0012) between the groups (Fig. 2b). In the placebo arm, daytime CSS exhibited minimal change, with a between-visit change of –0.027 (p = 0.45). Compared to placebo, daytime CSS in patients receiving flupentixol-melitracen decreased by 0.144 points over time (p = 0.0034). There was a significant Time × Condition interaction effects observed in the flupentixol-melitracen arm compared to placebo at T2 (B = –0.74, 95% CI [–1.20, –0.28], Z = 4.98, p = 0.034, d = –0.32) and T4 (B = –0.43, 95% CI [–1.20, –0.16], Z = 8.12, p = 0.0028, d = –0.75). However, the change in nighttime CSS over time was comparable between the groups (p = 0.87) and no differential Time × Condition effects were evident (Fig. 2c, Table 2).

The predefined subgroup analyses demonstrated consistent results with the primary endpoints. Significant differences from placebo in treatment response were observed in the subgroups of female patients (RR,

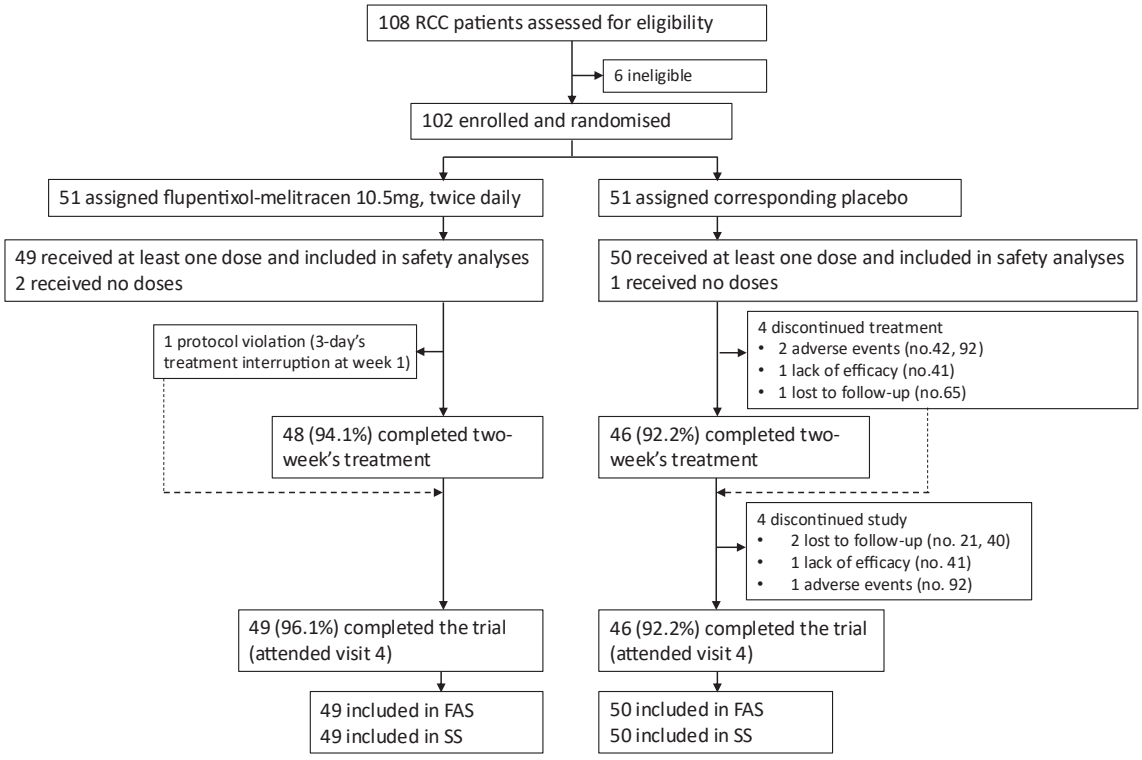

Fig. 1: Trial profile.

2.38 [95% CI: 1.25–4.53]; p = 0.0079), those aged ≥40 (RR, 2.05 [95% CI: 1.23–3.43]; p = 0.0046) and <50 years (RR, 2.82 [95% CI: 1.23–6.42]; p = 0.014), patients with a cough lasting at least two years (RR, 2.18 [95% CI: 1.18–4.03]; p = 0.013), baseline VAS ≥60 mm (RR, 2.35 [95% CI: 1.24–4.44]; p = 0.0094), baseline sum CSS ≥5 (RR, 2.50 [95% CI: 1.41–4.44]; p = 0.0011), baseline HARQ scored ≥14 (RR, 3.84 [95% CI: 1.31–11.24]; p = 0.014), and those with predominantly daytime cough (RR, 1.85 [95% CI: 1.13–3.02]; p = 0.014) (Fig. 3).

Secondary efficacy endpoints

Patients taking flupentixol-melitracen exhibited significant decreases in both VAS and HARQ scores over time compared to placebo. The VAS score in the flupentixol-melitracen arm showed a median decline of 30 points (IQR: 10–50) at T3 and 40 points (IQR: 10–60) at T4 from baseline, with a placebo-adjusted over-time change of −6.03 (95% CI: −9.12 to −4.00) (p = 0.0011) (Fig. 2d). At T3 and T4, a greater proportion of patients receiving flupentixol-melitracen experienced a VAS decrease of at least 30 mm compared to those receiving placebo (flupentixol-melitracen vs placebo: 69.4% [34/49] vs 24.0% [12/50] at visit three and 69.4% [34/49] vs 34.0% [17/50] at visit four) (Fig. 4a and b). The VAS scores in the flupentixol-melitracen arm showed a significant differential Time × Condition effects at T2 (B = −12.12, 95% CI [−15.80, −8.44], Z = 2.67, p = 0.0039, d = −0.25) and T4 (B = −6.98, 95% CI [−10.2, −3.76], Z = 1.28, p = 0.0061, d = −0.60) (Table 2). The HARQ score in the flupentixol-melitracen arm demonstrated a median decrease of 7.0 points (IQR: 1.5–12.0) from baseline at T4, with a placebo-adjusted over-time change of −0.76 (95% CI: −1.47 to −0.048) (p = 0.037) (Table 3). Although the LCQ score-indicated cough specific QoL did not show statistically significant change and Time × Condition effects over time relative to placebo, the improvement exceeded the minimal clinically important difference (1.3) in the flupentixol-melitracen arm at T3 (1.91 [IQR: 0.96–2.75]) and T4 (12.13 [IQR: 0.58–3.10]). Additionally, more patients receiving flupentixol-melitracen achieved an LCQ improvement of at least 1.3 points at both T3 and T4 (Fig. 4c and d). No notable differences and Time × Condition effects were observed in NLHQ score or depression and anxiety questionaries throughout the study (Supplementary Tables S2 and S3).

Complete case sensitivity analysis

To evaluate the robustness of our findings, we conducted a sensitivity analysis using the complete case dataset, excluding individuals with missing data on predictor variables. The primary outcomes (daytime

Clinical characteristics	Flupentixol-melitracen (N = 49)	Placebo (N = 50)	p-value
Age (years)	49.0 (15.7)	52.5 (14.7)	0.25
Body mass index (kg/m^2)	23.3 (3.4)	24.0 (2.9)	0.29
Sex			0.91
Female, n (%)	29 (59.2)	29 (58.0)	
Male, n (%)	20 (40.8)	21 (42.0)	
Duration of cough (months)	24.0 (12.0–72.0)	32.0 (9.5–72.0)	0.79
Cough phase			
Mainly during the day, n (%)	38 (77.6)	41 (82.0)	0.62
Mainly during the night, n (%)	3 (6.1)	6 (12.0)	0.49
No difference, n (%)	8 (16.3)	3 (6.0)	0.12
Cough nature			
Dry cough, n (%)	41 (83.7)	46 (92.0)	0.23
With sputum, n (%)	8 (16.3)	4 (8.0)	
Cough symptom score			0.23
Daytime	3.0 (3.0–4.0)	3.0 (3.0–4.0)	0.64
Nighttime	1.0 (1.0–1.0)	1.0 (1.0–1.5)	0.61
Visual analogue scale	70 (50–80)	75 (50–80)	0.88
FEV1%	100.9 (12.4)	99.7 (14.7)	0.70
FVC%	101.9 (13.7)	101.7 (16.4)	0.95
FEV1/FVC	84.0 (9.7)	83.8 (7.2)	0.91
FeNO (ppb)	13.5 (7.8–24.5)	19.5 (12.0–29.0)	0.094
PD20-FEV1 <7.8 mol, n (%)	1 (2.0)	1 (2.0)	1.0
Blood eosinophils	0.08 (0.04–0.19)	0.09 (0.07–0.14)	0.73
Sputum eosinophils% >2.5%, n (%)	2 (4.1)	2 (4.0)	1.0
Cough threshold			
C2 (μmol/L)	0.60 (0.14)	0.49 (0.10)	0.057
C5 (μmol/L)	0.82 (0.28)	0.52 (0.13)	0.11

Note: Data are expressed with mean (standard deviation [SD]), n (%), median (IQR), and geometric mean (SD), where appropriate. C2, minimum concentration of capsaicin required to elicit two coughs; C5, minimum concentration of capsaicin required to elicit five coughs; FAS, full analysis set; FEV1, forced expiratory volume in the first 1 s; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; PD20-FEV1, provocative dose resulting in 20% decrease in FEV1.

Table 1: **Demographic and clinical characteristics of the study participants included in the FAS.**

CSS and nighttime CSS) and the key secondary endpoint (VAS) demonstrated similar trends in over-time changes between the flupentixol-melitracen and placebo arms when comparing the two approaches to handling missing data (Supplementary Figure S2). GLMM analyses of the outcome variables at predefined timepoints produced results that were largely consistent with those obtained from the imputed dataset (Supplementary Table S4).

Safety

TEAEs were reported in 51.0% (25/49) of patients in the flupentixol-melitracen arm and 34.0% (17/50) of patients in the placebo arm (adjusted RR, 1.56 [95% CI: 0.88–2.77]; p = 0.087) (Table 4). Drowsiness was the most commonly reported TEAE, occurring in 32.7% (16/49) of the flupentixol-melitracen arm and 10.0% (5/50) in the placebo arm (RR, 1.86 [95% CI: 1.27–2.72]; p = 0.0058). Other TEAEs included insomnia (6.1% [3/49] vs 10.0% [5/50]), fatigue (4.1% [2/49] vs 2.0% [1/50]), and dizziness (4.1% [2/49] vs 6.0% [3/50]). All TEAEs were mild and resolved upon cessation of therapy.

Discussion

Findings from the present placebo-controlled RCT demonstrate that flupentixol-melitracen is effective in treating patients with RCC who are unresponsive to the currently available medications. A two-week treatment with flupentixol-melitracen resulted in cough resolution in 65.3% of patients with RCC by the end of the off-treatment safety follow up, accompanied by a gradual decrease in cough severity and an improvement in QoL.

The treatment of CC remains an unmet need. Opiates have long been used to manage cough, but they carry the potential for addiction and are strictly regulated. Among them, codeine, a prodrug of morphine, can be prescribed to cough patients in China, though its effectiveness largely depends on an individual's metabolic capacity. Several neuromodulators, such as gabapentin and baclofen, are commonly used off-label as antitussive agents; however, their efficacy is limited with tolerability issues. Non-pharmacological approaches, including speech pathology therapy, have demonstrated potential efficacy in several clinical trials, but are not likely to be pragmatic treatments in clinical settings due to the complexity in techniques.[30] The

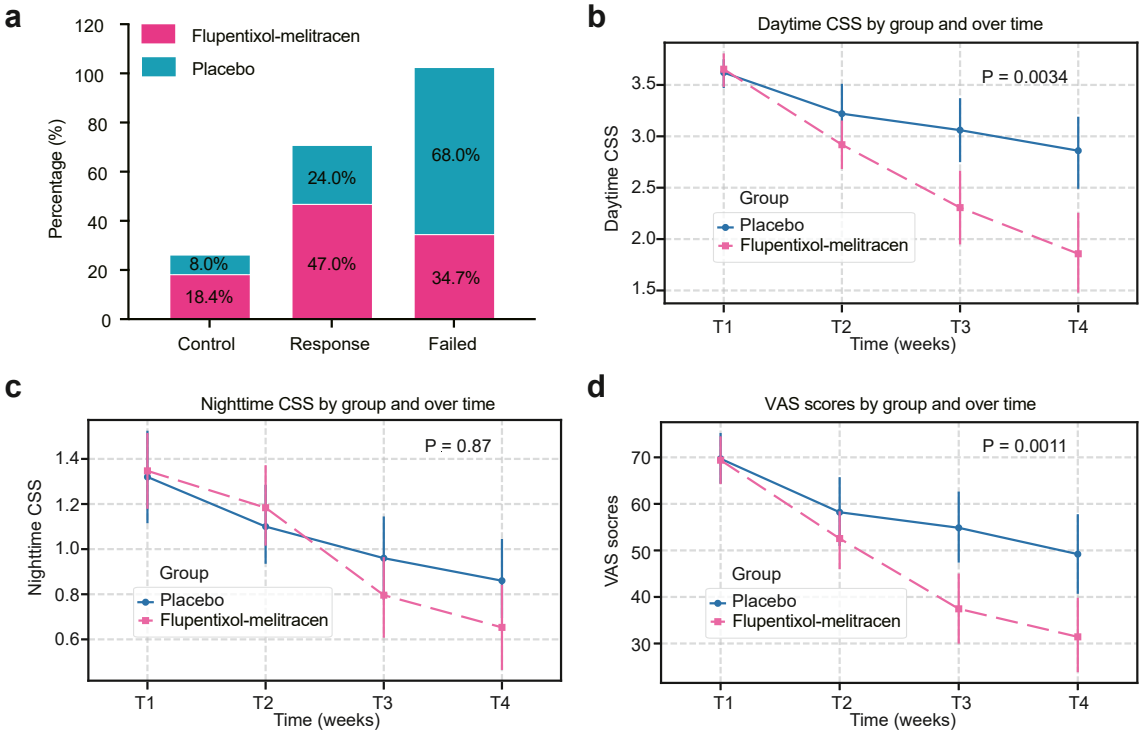

Fig. 2: Percentage of treatment response (a); over-time daytime CSS change (b), over-time nighttime CSS change (c), and over-time VAS change (d). The error bars represent the standard deviation (SD). CSS, cough symptom score; VAS, visual analogue scale.

Variables	Time points	Placebo	Flupentixol-melitracen	Time × Condition				
				Z	d	p-value	B	95% CI
Primary endpoints								
Daytime CSS	T1	4 (3–4)	4 (3–4)					
	T2	4 (3–4)	3 (2–4)	4.98	−0.32	0.034	−0.74	−1.20 to −0.28
	T3	4 (2–4)	2 (2–3)	0.49	−0.60	0.49	−0.25	−1.50 to 1.00
	T4	3 (2–4)	2 (1–3)	8.12	−0.75	0.0030	−0.43	−1.2 to −0.16
Nighttime CSS	T1	1 (1–1)	1 (1–2)					
	T2	1 (1–1)	1 (1–1)	2.41	−0.13	0.12	−0.29	−0.70 to 0.34
	T3	1 (1–1)	1 (0–1)	0.02	−0.23	0.88	−0.03	−0.55 to 0.35
	T4	1 (0–1)	1 (0–1)	2.11	−0.31	0.49	−0.21	−0.68 to 0.22
Key secondary endpoints								
VAS	T1	75 (52–80)	70 (50–80)					
	T2	60 (40–80)	50 (30–70)	2.67	−0.25	0.0039	−12.12	−15.80 to −8.44
	T3	60 (40–78)	30 (20–60)	0.002	−0.65	0.70	−0.36	−1.20 to 0.50
	T4	55 (10–77)	20 (10–60)	1.28	−0.60	0.0061	−6.98	−10.20 to −3.76
HARQ	T1	11 (7–16)	14 (8–18)					
	T2	8 (4–12)	12 (6–18)	9.53	−0.40	0.0020	−7.15	−10.50 to −3.80
	T3	9 (2–14)	7 (2–13)	0.62	−0.25	0.43	−1.82	−5.20 to 1.56
	T4	9 (2–16)	3 (1–9)	0.33	−0.45	0.24	−2.22	−6.80 to 0.36
LCQ	T1	17 (15–18)	16 (15–17)					
	T2	17 (16–18)	18 (17–19)	0.65	0.25	0.42	0.48	−0.15 to 0.65
	T3	17 (16–19)	19 (17–19)	0.07	0.55	0.79	−0.16	−0.30 to 0.80
	T4	18 (16–19)	19 (17–19)	0.25	0.45	0.58	0.37	−0.10 to 0.90

Note: Data are expressed with median (IQR). CI, confidence interval; CSS, cough symptom score; VAS, visual analogue scale; HARQ, Hull Airway Reflux Questionnaire; LCQ, Leicester Cough Questionnaire.

Table 2: **Model-based estimates and IQR for primary and key secondary outcomes at each time point for Flupentixol-melitracen vs Placebo.**

Secondary endpoints	Flupentixol-melitracen				Placebo				Change compared to placebo between visit over time (95% CI)	p-value
	T1	T2	T3	T4	T1	T2	T3	T4		
HARQ	14.0 (8.0, 18.0)	/	7.5 (2.0, 14.0)	6.0 (1.0, 13.0)	11.0 (7.0, 16.3)	/	9.0 (2.0, 14.0)	9.0 (1.5, 16.0)	−0.76 (−1.47 to −0.048)	0.037
Change from baseline	/	/	−6.0 (−9.0, −1.0)	−7.0 (−12.0, −1.5)	/	/	0.0 (−4.0, 0.0)	−1.0 (−4.5, 1.5)	/	/
LCQ	16.5 (14.9, 17.4)	/	18.1 (16.3, 19.1)	18.2 (16.4, 19.3)	17.1 (14.8, 18.2)	17.4 (15.5, 18.1)	17.6 (15.7, 18.7)	17.9 (15.5, 18.9)	0.15 (−0.06 to 0.36)	0.16
Change from baseline	/	/	1.9 (1.0, 2.8)	2.1 (0.6, 3.1)	/		0.8 (−0.2, 1.6)	0.8 (−0.4, 1.7)	/	/

Note: Data are expressed with median (IQR). CI, confidence interval; HARQ, Hull Airway Reflux Questionnaire; LCQ, Leicester Cough Questionnaire.

Table 3: **Summary of changes in HARQ and LCQ.**

development of novel antitussive drugs also faces challenges. Most cough clinical trials, particularly those involving treatment-naïve patients, have encountered varying magnitudes of placebo responses, ranging from minimal to nearly 70%.[8] The failure of gefapixant to gain regulatory approval from the U.S. Food and Drug

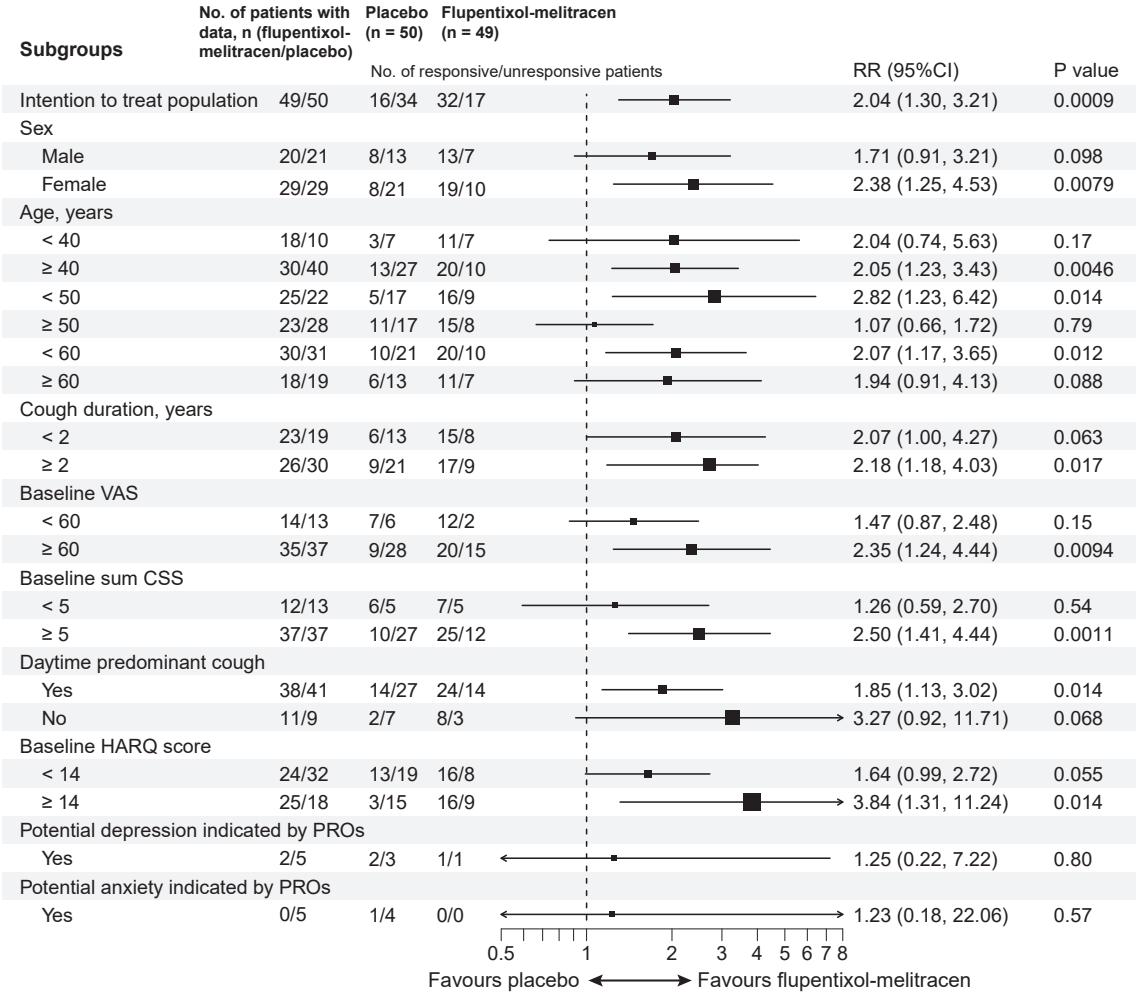

Fig. 3: Forest plot of pooled predefined subgroup analyses for primary endpoint. CSS, cough symptom score; VAS, visual analogue scale; HARQ, Hull Airway Reflux Questionnaire; PROs, patients' reported outcomes.

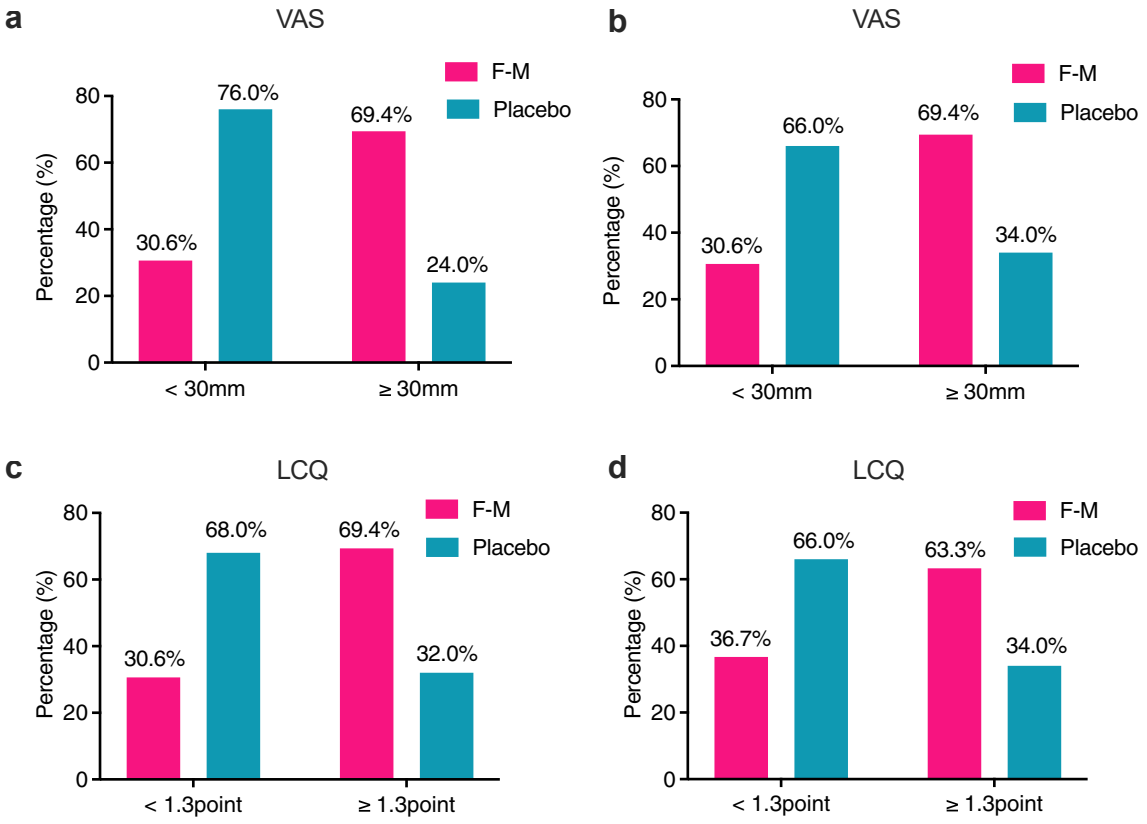

Fig. 4: Percentage of VAS reduction (<30 mm or ≥30 mm) (a and b) and LCQ improvement (<1.3-point or ≥1.3-point) (c and d) at T3 (a and c) and T4 (b and d) compared to baseline (observed in-trial data). At T3, 69.4% of patients receiving flupentixol-melitracen vs 24.0% of patients receiving placebo experienced a VAS decrease of at least 30 mm (a); 69.4% of patients receiving flupentixol-melitracen vs 32.0% of receiving placebo experienced an LCQ improvement of at least 1.3 points (c). At T4, 69.4% of patients receiving flupentixol-melitracen vs 34.0% of patients receiving placebo experienced a VAS decrease of at least 30 mm (b); 63.3% of patients receiving flupentixol-melitracen vs 34.0% of patients receiving placebo experienced an LCQ improvement of at least 1.3 points (d). LCQ, Leicester Cough Questionnaire; VAS, visual analogue scale.

TEAEs, n (%)	Flupentixol-melitracen (N = 49)	Placebo (N = 50)	Effect size (95% CI)	p-value
Any TEAEs	25 (51.0)	17 (34.0)	ARR, 1.56 (0.88–2.77)	0.087
Drowsiness	16 (32.7)	5 (10.0)	ARR, 1.86 (1.27 to 2.72)	0.0058
Insomnia	3 (6.1)	5 (10.0)	ARR, 0.85 (0.34 to 2.14)	0.72
Fatigue	2 (4.1)	1 (2.0)	ARR, 1.26 (0.37–4.28)	0.62
Dizziness	2 (4.1)	3 (6.0)	ARR, 0.42 (0.086–2.09)	1.0
Restless	2 (4.1)	0	ARR, 2.06 (1.68–2.53)	0.24
Impotence	1 (2.0)	0	ARR, 1.00 (0.28–3.50)	0.50
Headache	1 (2.0)	1 (2.0)	ARR, 1.64 (0.64–4.16)	1.0
Nausea	1 (2.0)	2 (4.0)	ARR, 0.81 (0.13–5.03)	1.0
Dry pharynx	1 (2.0)	0	ARR, 2.04 (1.67–2.50)	0.50
Dry mouth	1 (2.0)	1 (2.0)	ARR, 0.32 (0.13–0.80)	1.0
Hypertension	0	1 (2.0)	Unadjusted RR, 2.00 (1.64–2.44)[a]	1.0
Lack of appetite	0	1 (2.0)	Unadjusted RR, 2.00 (1.64–2.44)[a]	1.0
Stomach discomfort	0	1 (2.0)	Unadjusted RR, 2.00 (1.64–2.44)[a]	1.0
Diarrheal	0	1 (2.0)	Unadjusted RR, 2.00 (1.64–2.44)[a]	1.0

Note: ARR, adjusted risk ratio; RR, risk ratio. Unadjusted risk difference was reported [a]Risk ratio was not measurable since the adverse event rate was 0 in the Flupentixol-melitracen group.

Table 4: **Summary of any treatment-emergent adverse events (TEAEs).**

Administration is a notable example (https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-17-2023-meeting-pulmonary-allergy-drugs-advisory-committee-11172023), although it has licenced in Europe and Japan due to its promising antitussive effect shown in two largest global cough trials. In the present placebo-controlled trial, most patients were referred from the primary healthcare and all had low expectations of treatment success since they had undergone at least two weeks of treatment with at least one neuromodulator without any therapeutic response. The placebo response was observed in only 32.0% of patients, while the treatment efficacy of flupentixol-melitracen exceeded 60%. These results provide relatively reliable evidence supporting the antitussive effect of flupentixol-melitracen and further confirm the potential antitussive effect we reported previously.[11]

A substantial body of evidence from both preclinical and clinical studies has shown that CC is a neuronal disorder and the underlying mechanism involves both peripheral and central neuronal pathways.[31] Alterations in the quantity or activity of the neurotransmitters, such as dopamine, serotonin and norepinephrine, which mediate synaptic signal transmission between neurons, are closely associated with the cough reflex hypersensitivity.[32] Flupentixol is a postsynaptic dopamine D1 and D2 receptor antagonist that exerts its antipsychotic effects by blocking dopamine D2 receptors in the brain and increasing the amount of dopamine in the synaptic gap. Melitracen is a tricyclic antidepressant that works by blocking the reuptake of serotonin and norepinephrine at presynaptic terminals. The combination of flupentixol and melitracen was designed to work synergistically, minimising the side effects of each component, with properties that can treat various psychiatric and mental conditions. Although the mental health condition can interact with CC, only five patients in the present study were considered to have depression or anxiety. Given that subgroup analyses also suggested no relationship between treatment response and baseline mental health and that the overall mental health scores remained stable throughout the trial, it is unlikely that the antitussive effect of flupentixol-melitracen is attributable to its anxiolytic and antidepressant properties. Instead, the increased levels of dopamine, serotonin, and norepinephrine resulting from flupentixol-melitracen are likely to contribute directly to cough alleviation by reducing the central cough sensitivity on their own rights. Indeed, the ability of flupentixol-melitracen to reverse abnormal central neural activity has been visualised using functional magnetic resonance imaging in patients with irritable bowel syndrome.[33] The decreased capsaicin cough sensitivity observed in our previous work suggests that flupentixol-melitracen may also act through the peripheral pathways.[11] This peripheral action of flupentixol-melitracen is also evidenced by its ability to improve gastrointestinal symptoms in functional dyspepsia patients.[34,35] Since oesophagus dysmotility has been reported in over two-thirds of CC patients,[36] we theorise that flupentixol-melitracen my also work by directly or indirectly regulating neurotransmitters in the gut, thereby raising the cough threshold through improved gut function and reduced airway reflux.

Similar to the previous observations where flupentixol-melitracen maintained effective during the four-week dose reduction period following a four-week treatment course,[11] a further trend toward improvement in CSS was also observed by the end of the off-treatment safety follow up in the present study, as well as in the VAS and HARQ scores. Although the placebo-adjusted change in LCQ did not achieve statistical significance in absolute value, approximately two-thirds of patients taking flupentixol-melitracen experienced an LCQ improvement above the minimal clinically important difference at both the end of treatment and the end of the safety follow up.[37] Although sensitivity analyses of the key outcomes indicated that our results were robust to factors associated with missing data, the effect estimates may still be subject to overestimation. A longer treatment period may cause greater benefit. Subgroup analyses indicated females and those aged between 40 and 50 years, particularly those with a more severe daytime cough or a cough lasting at least two years, are more likely to respond to flupentixol-melitracen. Daytime-predominant cough is a typical feature of RCC, with most patients coughing less or not at all during the night. This likely explains why nighttime cough severity did not change significantly throughout the trial and remained comparable between groups.

One might raise safety concerns about administering flupentixol-melitracen to cough patients. Indeed, approximately half of the participants who received flupentixol-melitracen in the present study experienced TEAEs. However, drowsiness was the only TEAE reported more frequently than in the placebo cohort. Based on findings from the present trial and previous observations, all reported adverse events during the short-term use of flupentixol-melitracen in cough patients were manageable and reversible. In a real-world study comparing the clinical practice of gabapentin, baclofen, and flupentixol-melitracen in the management of patients with RCC, the overall incidence of adverse events with flupentixol-melitracen (22.0%) was slightly lower than with the other two drugs (28.3% for gabapentin and 32.3% for baclofen).[7] Therefore, for patients who are unresponsive to all existing treatments, the short-term use of flupentixol-melitracen can be considered. Further studies are needed to evaluate the risk–benefit profile of flupentixol-melitracen and to determine its optimal treatment duration and dosage for patients with RCC.

This study has several major limitations. The first is the absence of an objective endpoint. Due to the unavailability of cough counters, cough frequency, a fundamental metric that regulatory authorities prioritise for drugs seeking marketing approval, was not employed. This study primarily aimed to provide evidence for an additional treatment option for patients unresponsive to existing therapies, with emphasis on the patients' feelings. Cough frequency exhibits significant daily variability and poorly correlates with subjective PROs.[38] It does not fully shed light on patients' experiences. The same limitation applies to the capsaicin challenge test, which was not repeated at the end of this short-duration study. However, to comprehensively establish the efficacy profile of flupentixol-melitracen, future studies employing objective cough counting will be undertaken once cough counters are available in our department. Secondly, despite the study being conducted in a double-blinded manner, there is a risk of unblinding that could amplify the therapeutic response, because a considerable proportion of patients may be aware of their treatment due to the occurrence of frequent adverse events. Thirdly, the methodological limitations should be considered, including measurement bias and selection bias in the mITT estimates and selection bias due to missing outcome data, which may influence the interpretation and generalizability of our results.[37] Some subgroup analyses, particularly those involving subgroups with few participants or rare events (e.g., subgroups with zero or one event in a single arm), are susceptible to sparse data bias. This may lead to unstable estimates of RR and overly wide 95% CIs.[39] Finally, patients included in this study reported better quality of life compared to those in COUGH-1 and COUGH-2,[40] likely representing a milder patient population. Additionally, long-term effects were not assessed. Although therapeutic effects usually appear within one to five days in responders, long-term studies with robust designs involving broader populations (including those aged over 70) are needed to address unanswered questions regarding safety, tolerance, and optimal treatment regimen.

In conclusion, this placebo-controlled study shows a significant therapeutic response of flupentixol-melitracen in the short-term management of RCC. Flupentixol-melitracen is associated with improvements in cough symptoms and cough-specific QoL for short-term use, independent of the presence of mental health illness. Future studies are required to further evaluate the risk–benefit profile for its longer-term use.

Contributors

ZQ and KL conceived, designed, and planned this study. QC, MZ, LZ, AA, RD, XX, and LY collected and acquired the data. MZ and LZ analysed the data. QC, MZ, LZ, AA, and ZQ interpreted the data. QC, MZ, LZ, and AA drafted the manuscript. QC, MZ, LZ, AA, RD, XX, LY, KL, and ZQ critically reviewed and revised the manuscript. QC, MZ, LZ, AA, RD, XX, LY, KL, and ZQ had full access to and verify the underlying study data. ZQ and KL accept responsibility to submit for publication.

Data sharing statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request or via sending an email to M.Zhang2@hull.ac.uk or Lesiazhang_66@163.com.

Declaration of interests

All authors have completed the International Committee of Medical Journal Editors (ICMJE) uniform disclosure form and declare no competing interests.

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We respectfully acknowledge the contribution of Professor Zhongmin Qiu, who sadly passed away on 24 December 2024 at 12:27. His invaluable guidance and expertise greatly enriched this work, and he is deeply missed.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103367.

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