DynaMed Plus®

Critical Appraisal Practicum

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What we'll talk about today:

- DynaMed process for appraising randomized trials and writing evidence summaries about treatment efficacy
- Background
  - Levels of Evidence (LOE)
  - Quality Criteria
  - Summary Structure
- Example
  - How the critical appraisal process is reflected in the study summary
- Hands-on practice and Discussion

Levels of Evidence

LOE: a 3-tiered system for categorizing the validity of evidence based on the Strength of Recommendation Taxonomy (SORT)

Level 1 (likely reliable) Evidence

- methodologically rigorous randomized trials and systematic reviews that address **patient-oriented** (clinical) outcomes judged to be free of significant sources of bias

Level 2 (mid-level) Evidence

- Studies addressing **patient-oriented** outcomes, using a method of scientific comparison, but including ≥ 1 major potential bias

Level 3 (lacking direct) Evidence

- Studies (including RCTs) with surrogate outcomes only
- Reports based on uncontrolled analysis of patient-oriented outcomes (*e.g.* case series)

Critical Appraisal

- Systematic evaluation of the methodologic quality of a study to identify any sources of potential bias that may limit the validity of the findings

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- ***DynaMed* criteria for level 1 (likely reliable) evidence for interventional conclusion (conclusions that an intervention does or does not change an outcome)**
    1. Full-text report available in English (or language well understood by participating editor)
    2. Clinical outcome (also called patient-oriented outcomes)
    3. Population, intervention, comparison, and outcome in the study is representative of expected clinical practice
    4. Random allocation method (i.e. not assigned by date of birth, day of presentation, “every other”)
    5. Blinding of all persons (patient, treating clinician, outcome assessor) if possible
    6. Follow-up (endpoint assessment) of at least 80% of study entrants AND adequate such that losses to follow-up could not materially change the results
    7. Accounting for dropouts (even if not included in analysis)
    8. Adequate precision of effect estimate based on
        1. Confidence intervals do not include both presence of no effect (relative risk 0.9-1.1) and presence of substantial relative effect (such as relative risk <0.75 or >1.25)
        2. Adequate power (based on sample size and observed control event rate) to detect clinically important differences
    9. Consistency of findings across measures of similar outcomes
    10. In cases of randomized parallel-group trials
        - Allocation concealment
        - Intention-to-treat analysis comparing groups according to randomization
    11. No other factors contributing to substantial bias, such as
        - Differences in management between groups other than the intervention being studied
        - Differential loss to follow-up
        - Posthoc analysis
        - Subgroup analysis
        - Baseline differences between groups
        - Unclear how missing data are accounted for if possible

Critical Appraisal

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Threats to Validity

- Trial design weaknesses
- Procedural concerns
- Statistical analysis issues

Critical Appraisal: Threats to Validity

- Trial Design Weaknesses
  - Lack of allocation concealment
  - Lack of blinding of patients and study personnel (when possible)
  - Sample size < 30 patients per group
- Procedural Concerns
  - Baseline differences between groups
  - High rates of dropout or loss to follow-up (> 20%)

Critical Appraisal: Threats to Validity

- Statistical Analysis Issues
  - Lack of intention-to-treat analysis
  - Post hoc analysis
  - Confidence Intervals that indicate imprecise effect estimates
    - Non-significant results with wide CIs
    - Skewed CIs including both clinically important and unimportant results
  - Statistically significant results without clear clinical importance

The DynaMed Summary

- LOE is reflected in the phrasing of the summary conclusion.

- LOE1 vs. LOE2: sure, assertive statement vs. provisional statement
  - LOE1: **intervention X reduces pain**
  - LOE2: **intervention X may reduce pain**

- The DynaMed Conclusion
  - may not agree with the author's conclusion
  - may highlight outcomes other than those considered most important by the authors

The DynaMed Summary

- When we downgrade from LOE1, we have to explain why
  - presented on the second line of the summary (basis statement)
- Only a single downgrade reason is needed
  - additional concerns can be addressed in the body of the summary.
  - But multiple flaws does not mean further downgrading!
- The downgrade reason identifies the potential bias that is most relevant to the conclusion being drawn.
- Frequently the downgrade requires additional explanation in the body of the summary.

Indian J Pediatr. 2011 Jul;78(7):801-6. Epub 2011 Feb 2.

Unsynchronized Nasal Intermittent Positive Pressure Ventilation to prevent extubation failure in neonates: a randomized controlled trial.

Abstract

OBJECTIVE:
To evaluate the role of Unsynchronized Nasal Intermittent Positive Pressure Ventilation (NIPPV) in prevention of extubation failure in mechanically ventilated preterm neonates weighing less than 2,000 g.

METHODS:
This randomized controlled trial was conducted in the neonatal intensive care unit of a tertiary care teaching hospital. Preterm neonates weighing less than 2,000 g, mechanically ventilated for more than 24 h were included after extubation. Neonates were randomized into two groups. Group 1 was given unsynchronized nasal intermittent positive pressure ventilation with shortened endotracheal tube by ventilator and Group 2 was given head box oxygen, fraction of oxygen in inspired air was 50%. Primary outcome variable was rate of extubation failure within 72 h of extubation.

RESULTS:
Birth weight, gestational age, age at intubation, indication for mechanical ventilation and antenatal details were comparable in the two groups. Extubation failure rate was 16% in Group 1 vs, 63% in Group 2 (RR = 0.25; 95% CI: 0.12, 0.51, p value = 0.00), that is a reduction of 47%.Unsynchronized nasal intermittent positive pressure ventilation did not have any serious side effects, however it did not reduce total hospital stay.

CONCLUSIONS:
Unsynchronized Nasal Intermittent Positive Pressure Ventilation is a simple technique of noninvasive ventilation which significantly reduces the rate of extubation failure in preterm neonates and is not associated with serious side effects.

PMID: 21287368

Patient:	**preterm neonates (weighing < 2000 g and mechanically ventilated)**
Intervention:	**unsynchronized nasal intermittent positive pressure ventilation (UNIPPV)**
Comparison:	**head box oxygen**
Outcome:	**extubation failure rate was 16% vs. 63%**

- So, results suggest that UNIPPV reduces extubation failure in preterm neonates compared to head box oxygen.

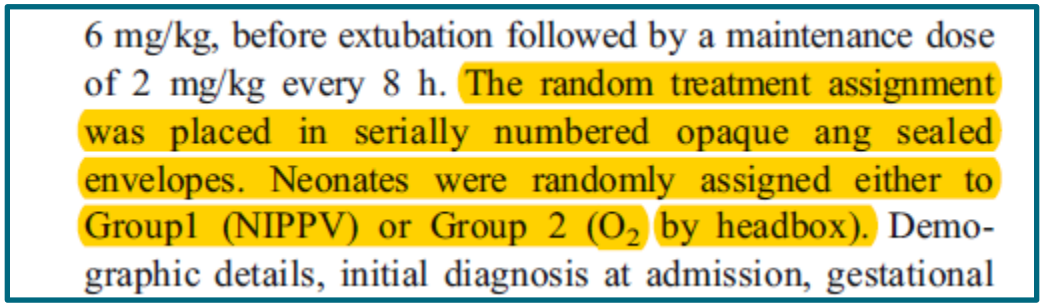
- How confident are we in this trial's demonstration of that outcome?
  (Does it meet LOE 1 criteria?)

Patient oriented outcome? YES (extubation failure)

Not LOE 3!

Can be LOE 1 or LOE 2

Allocation concealed ? YES

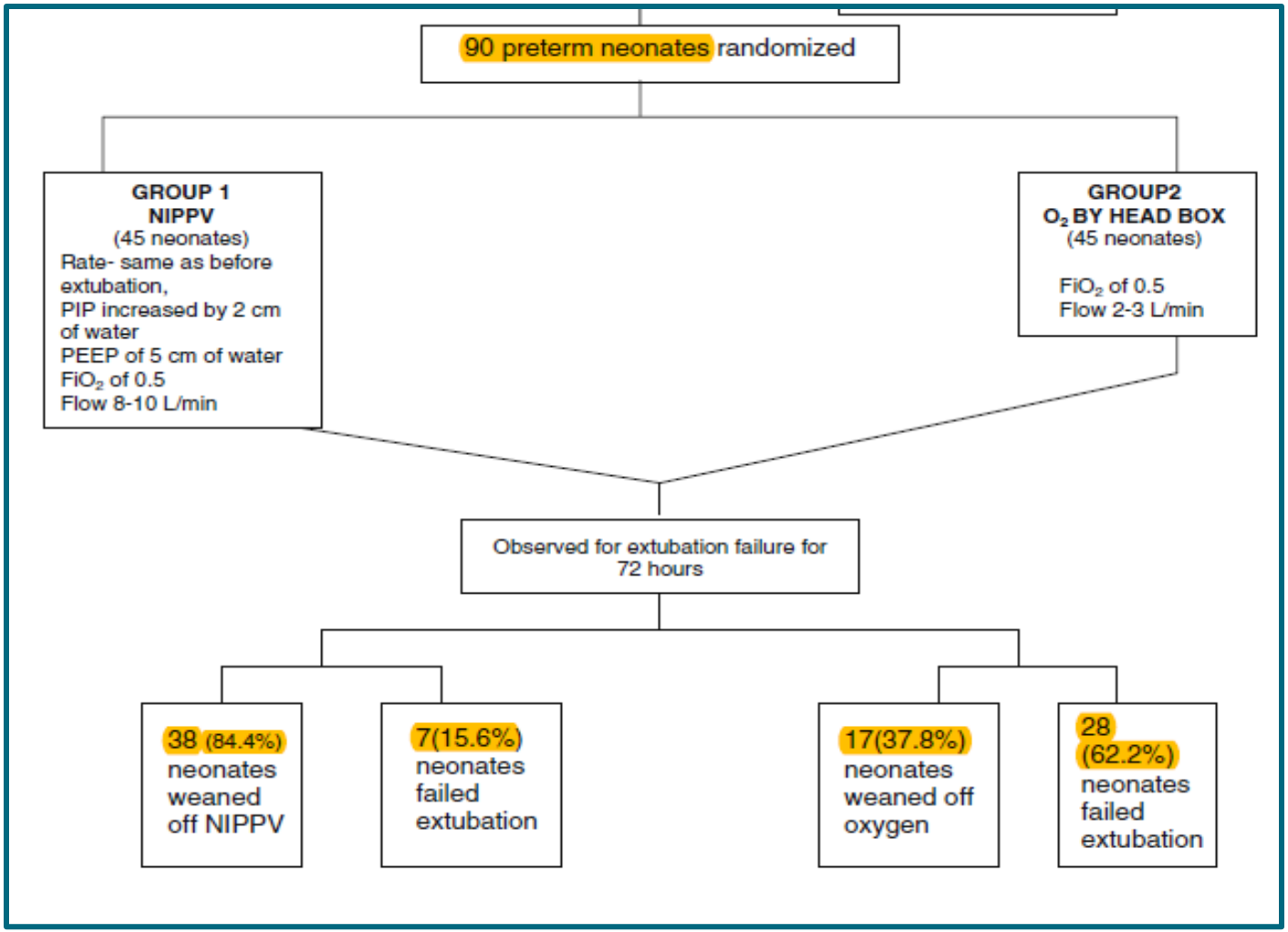


6 mg/kg, before extubation followed by a maintenance dose of 2 mg/kg every 8 h. The random treatment assignment was placed in serially numbered opaque ang sealed envelopes. Neonates were randomly assigned either to Group1 (NIPPV) or Group 2 (O_2 by headbox). Demographic details, initial diagnosis at admission, gestational

Blinded ? NO

(but could it be? In theory, outcome assessors could have been blinded. They weren't but the outcomes being assessed are objective)

Adequate Sample size (> 30 / group)	YES
Adequate follow-up (> 80%)	YES
Intention-to-Treat Analysis?	YES



Baseline Differences?

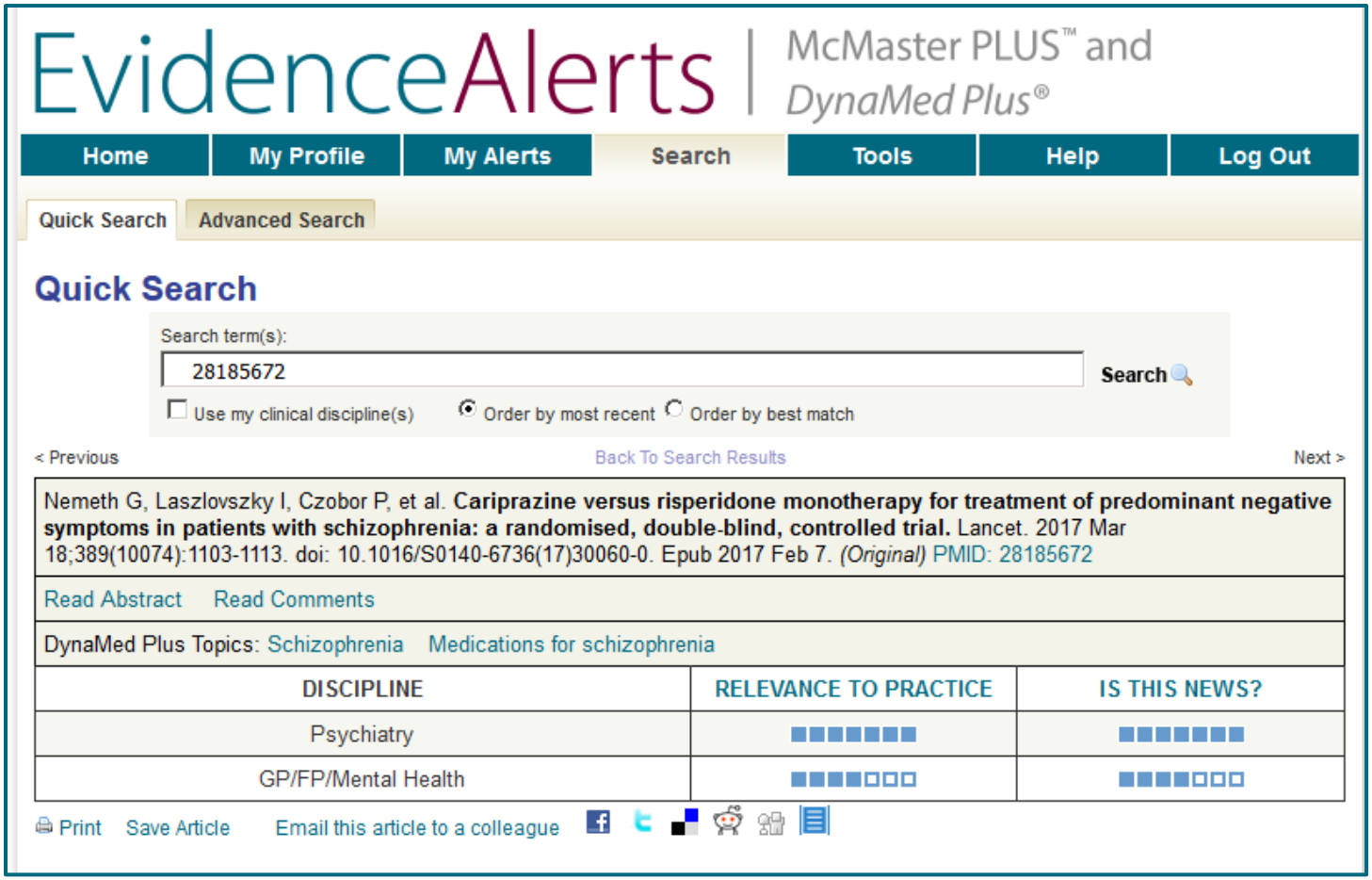
Table 1 Demographic and baseline variables of neonates

	No. of neonates in NIPPV Group (45)(%)	No. of neonates in 'O_2 by headbox' Group(45)(%)	*P* value
Gestational age(wks)(mean±SD)	31±2.7	31±3.1	0.30
Birth weight(gm)(median)	1,367	1,339	0.7
Male sex	33(73.33)	26(57.77)	0.09
Adequate ANC	19(42.22)	26(57.7)	0.14
Antenatal steroid	6(13.3)	12(26.6)	0.18
Surfactant therapy	6(13.33)	8(17.77)	0.56
Indication for MV			0.68
Pneumonia	14(31.11)	16(35.55)	
Apnoea	16(35.55)	12(26.66)	
Poor respiratory effort	7(15.5)	5(11.11)	
HMD	8(17.77)	12(26.6)	
Age at intubation(days)(mean±SD)	5.06±5.01	5.26±6.4	0.31
Age at extubation(days)(mean±SD)	9.55±6.44	8.35±7.25	0.09
Duration of MV (hours)(mean±SD)	106.46±89.82	80.22±73.11	0.01
Resuscitation at birth:			0.95
Oxygen	15(33.33)	17(37.77)	
Tactile stimulation	2(4.44)	2(4.44)	
BMV	3(6.66)	2(4.44)	
IPPR	7(15.55)	5(11.11)	
Hb at extubation(gm)	16.2	16.45	0.43
Positive blood culture	18(40)	27(60)	0.06
Positive ET tip culture	44(97.7)	45(100)	0.31

DMP Summary

- **unsynchronized nasal intermittent positive pressure ventilation may reduce need for reintubation in preterm neonates weighing < 2 kg (4.4 lbs) (level 2 [mid-level] evidence)**
  - based on randomized trial with baseline differences
  - 90 preterm neonates (mean gestational age 31 weeks) weighing < 2 kg (4.4 lbs) randomized after extubation to unsynchronized nasal intermittent positive pressure ventilation (UNIPPV) vs. oxygen by head box (fraction of oxygen in inspired air 50%)
  - all infants had mechanical ventilation for > 24 hours prior to baseline
  - baseline differences comparing UNIPPV group vs. head box oxygen group
    - mean duration of mechanical ventilation 106.4 hours vs. 80.2 hours (p = 0.01)
    - positive blood culture in 40% vs. 60% (p = 0.06)
  - comparing UNIPPV vs. head box oxygen
    - need for reintubation within 72 hours in 15.6% vs. 62.2% (p < 0.01, NNT 3)
    - mean hospital stay 16 days vs. 20 days (not significant)
  - UNIPPV associated with increase in nasal trauma and agitation (p = 0.04 for each)
  - Reference - Indian J Pediatr 2011 Jul;78(7):801

Your Turn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Nemeth G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. Lancet. 2017 Mar 18;389(10074):1103-1113. doi: 10.1016/S0140-6736(17)30060-0. Epub 2017 Feb 7. (Original) PMID: 28185672
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Critical Appraisal of a Randomized Trial

Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial

Reference - Lancet 2017 Mar 18;389(10074):1103

- What conclusion do you draw?
- How confident are you?
- Why?

Concerns?

- Discontinuation rates?
  - 22.6% overall
  - Are they different between groups?
  - Were patients who discontinued included in analysis?
  - Only 3 patients lost to follow-up
- Effect size?
- Anything else?

Results

- Mean Reduction in PANSS negative symptom scores
  - 8.63 with cariprazine vs. 7.16 with placebo
  - mean difference 1.48 (95% CI 0.57-2.38), p = 0.0015
  - Is this difference clinically important?
  - Cohen's *d* = (7.16 - 8.63)/4.98257 = 0.295 (small to moderate effect)

- Response Rate (≥ 20% reduction in PANSS negative symptom score)
  - 69% vs. 58% (95 % CI for difference 2.3%-19.9%) (p = 0.014 by raw numbers, simple OR 1.6)
  - (repeated measures OR 2.08, p = 0.0022)

DMP Summary

If conclusion is based mostly on the primary outcome:

- **cariprazine monotherapy may improve negative symptoms compared to risperidone monotherapy in adults with stable schizophrenia with predominantly negative symptoms but without depression (level 2 [mid-level] evidence)**
  - based on randomized trial with confidence interval including differences that may not be clinically important
  - 461 adults ≤ 65 years old (median age 40 years) with stable schizophrenia > 2 years and predominantly negative symptoms (blunted affect, emotional withdrawal, passive or apathetic social withdrawal, lack of spontaneity) > 6 months were randomized to cariprazine vs. risperidone for 26 weeks
    - cariprazine starting dose 1.5 mg/day orally titrated to target dose 4.5 mg/day over 14 days (maximum dose 6 mg/day)
    - risperidone starting dose 2 mg/day orally titrated to target dose 4 mg/day over 14 days (maximum dose 6 mg/day)
  - patients excluded for moderate-to-severe depressive symptoms or use of antidepressant within 3 months
  - primary outcome was PANSS negative symptom score (range 7-49 points, with higher score indicating worse symptom severity)
  - mean PANSS negative symptom scores at baseline were 27.7 in cariprazine group and 27.5 in risperidone group
  - 23% discontinued trial medication in each group, and 99% included in analyses
  - comparing cariprazine vs. risperidone at 26 weeks
    - mean reduction in PANSS negative symptom score 8.63 points vs. 7.16 points (95% CI for difference 0.57-2.38 points), significant but CI includes differences that may not be clinically important
    - adverse events in 53% vs. 57% (no p value reported)
  - cariprazine also associated with significant improvements in psychosocial functioning on Personal and Social Performance Scale
  - treatment-emergent adverse events included insomnia, headache, akathisia, and anxiety
  - Reference - Lancet 2017 Mar 18;389(10074):1103, editorial can be found in Lancet 2017 Mar 18;389(10074):1077

DMP Summary

If conclusion is based mostly on the secondary dichotomous outcome:

- **cariprazine monotherapy improves negative symptoms compared to risperidone monotherapy in adults with stable schizophrenia with predominantly negative symptoms but without depression (level 1 [likely reliable] evidence)**
  - based on randomized trial
  - 461 adults ≤ 65 years old (median age 40 years) with stable schizophrenia > 2 years and predominantly negative symptoms (blunted affect, emotional withdrawal, passive or apathetic social withdrawal, lack of spontaneity) > 6 months were randomized to cariprazine vs. risperidone for 26 weeks
    - cariprazine starting dose 1.5 mg/day orally titrated to target dose 4.5 mg/day over 14 days (maximum dose 6 mg/day)
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  - mean PANSS negative symptom scores at baseline were 27.7 in cariprazine group and 27.5 in risperidone group
  - 23% discontinued trial medication in each group, and 99% included in analyses
  - comparing cariprazine vs. risperidone at 26 weeks
    - ≥ 20% improvement in PANSS negative symptom score in 69% vs. 58% (p = 0.0022, NNT 9)
    - mean reduction in PANSS negative symptom score 8.63 points vs. 7.16 points (p = 0.0015)
    - adverse events in 53% vs. 57% (no p value reported)
  - cariprazine also associated with
    - significant improvements in psychosocial functioning on Personal and Social Performance Scale
    - significantly higher rate of ≥ 30% improvement in PANSS negative symptom score in post hoc analysis
  - treatment-emergent adverse events included insomnia, headache, akathisia, and anxiety
  - Reference - Lancet 2017 Mar 18;389(10074):1103, editorial can be found in Lancet 2017 Mar 18;389(10074):1077

THANK YOU

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