ABSTRACT

Introduction Neurodevelopmental disorders are a group of disorders thought to be associated with the functioning of the brain and the nervous system. Children with neurodevelopmental disorders often have sleep-related comorbidities that may negatively affect quality of life for both the children and their families. Melatonin is one of the most used interventions in children with neurodevelopmental disorders and sleep disorders. Previous reviews have investigated the effects of melatonin for sleep disorders in children with neurodevelopmental disorders, but these had important limitations, such as inadequate analysis of adverse effects, small sample sizes and short follow-up.

Methods and analysis This is a protocol for a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials. The protocol is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols. We will search for published and unpublished trials in the Cochrane Central Register of Controlled Trials, MEDLINE Ovid, Embase Ovid, LILACS, Science Citation Index Expanded, Conference Proceedings Citation Index-Science, PsyCINFO, ClinicalTrials.gov and the International Clinical Trials Registry Platform. We will search the databases from their inception without language restrictions. We will also request clinical study reports from regulatory authorities and pharmaceutical companies. Review authors working in pairs will screen reports, extract data and conduct risk of bias assessments using the Cochrane Risk of Bias tool. We will include randomised clinical trials comparing melatonin versus placebo or no intervention for sleep disorders in children with neurodevelopmental disorders. Primary outcomes will be total sleep time and adverse effects. Secondary outcomes will be quality of life of the child and caregivers and sleep onset latency. Data will be analysed using random-effects and fixed-effect meta-analyses. Certainty of evidence will be assessed with Grading of Recommendations, Assessment, Development and Evaluation approach.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The methodology of our systematic review is pre-defined in detail to avoid data-driven biased results.
⇒ The protocol is based on the Cochrane Handbook, the eight-step procedure suggested by Jakobsen et al, Trial Sequential Analysis and the Grading of Recommendations, Assessment, Development and Evaluation approach.
⇒ This systematic review will consider the risks of random errors, systematic errors, publication bias, heterogeneity and external validity.
⇒ This systematic review will include both published and unpublished trials.
⇒ We assess multiple outcomes and subgroup analyses which increases the risks of type I errors.

INTRODUCTION

Description of the condition Neurodevelopmental disorders are a group of disorders thought to be associated with the functioning of the brain and the nervous system.1 Neurodevelopmental disorders are usually diagnosed in childhood and include neurological disorders such as cerebral palsy, epilepsy, Angelman syndrome, Down’s syndrome, Fragile X syndrome, Prader-Willi syndrome, Rett syndrome, Smith-Magenis syndrome, Williams syndrome and non-specific intellectual disability, along with some psychiatric disorders including autism spectrum disorder, attention deficit hyperactivity
disorder (ADHD) and attention deficit disorder (ADD). Children with neurodevelopmental disorders may experience difficulties with learning, attention, behaviour, speech, motor skills and other neurological functions.

The impact of sleep disturbances was recently ranked as a top 10 research priority within the topics of children with neurodevelopmental disorders by a UK partnership of patients, carers and clinicians. Children with neurodevelopmental disorders often have sleep-related comorbidities, including sleep disorders such as insomnia disorder, hypersomnia, narcolepsy, breathing-related sleep disorders, circadian rhythm sleep disorders, rapid eye movement (REM) sleep arousal disorders, non-REM sleep arousal disorders and nightmare disorders. Studies have shown the prevalence of comorbid neurodevelopmental disorders and sleep disorders is between 25% and 86% compared with 1% and 6% in the general paediatric population. Sleep disorders may further enhance problems with learning and behaviour in children with neurodevelopmental disorders, and often have a negative effect on quality of life for both the children and their families.

Description of the intervention
Melatonin is a naturally occurring hormone in both humans and animals. Previously, melatonin was derived from animal pineal tissue, but it is now developed synthetically and distributed in different forms, including capsules, tablets, gummies and liquids. Melatonin is available in many countries either sold as prescription-only medicine or as over-the-counter medicine to treat sleep disorders in both children and adults, as it is hypothesised to be associated with few adverse effects. Furthermore, melatonin is one of the most commonly used interventions in children with neurodevelopmental disorders and sleep disorders. The dosage recommendations vary according to country, but the UK National Health Service currently recommend treatment up to 13 weeks of 2 mg 1–2 hours before bedtime for adults with sleep problems. However, there are currently no clear guidelines for prescribing melatonin for children and adolescents with neurodevelopmental disorders.

How the intervention might work
The understanding of melatonin’s underlying mechanisms has previously been extrapolated from animals to humans, but the exact physiological mechanisms of melatonin in humans remain unclear. Melatonin is a neurohormone primarily secreted by the pineal gland. Melatonin mediates dark signals, since the secretion of melatonin is related to darkness, and it is therefore associated with the circadian rhythm in humans. The secretion of melatonin is regulated by the suprachiasmatic nucleus in the hypothalamus, and the production of melatonin depends on darkness, as the exposure to light inhibits secretion. A decrease in the secretion of melatonin has been associated with ageing and different diseases, and synthetic melatonin may theoretically reduce sleep disturbance related to melatonin deficiency. Previous studies have shown that melatonin improves total sleep time, sleep onset latency and sleep quality for adults with sleep disorders, but the effects seem small. Furthermore, some studies suggest that children with autistic spectrum disorders have abnormal secretions of melatonin. For these theoretical reasons, children with neurodevelopmental disorders may benefit from melatonin.

Why it is important to do this review
A systematic review published in 2018 investigated the effects of melatonin for sleep problems in children with neurodevelopmental disorders. The review concluded that melatonin was safe and effective in improving sleep for children with neurodevelopmental disorders. Another systematic review published in 2019 investigated the effects of oral melatonin for non-respiratory sleep disturbances in children with neurodisabilities. The review concluded that there was some evidence of beneficial effects, but the extent of these effects was unclear due to the poor quality of the evidence. The review also concluded that melatonin was well-tolerated, as comparable adverse effects were found in the melatonin and placebo groups.

These previous reviews had important limitations. The conclusions were affected by a high degree of heterogeneity, high and unclear risk of bias in the included trials and small sample sizes. Furthermore, the duration of treatment was limited to a maximum of 13 weeks, and adverse events were not adequately reported or analysed in either of the reviews.

In recent studies, it has been questioned whether higher levels of melatonin are associated with delayed puberty, and other adverse effects of melatonin are also theoretically possible. In 2021, a 2-year follow-up of a trial investigating the treatment with melatonin in 119 children with autism spectrum disorder was published. This trial concluded that melatonin was safe and effective for long-term treatment in children. Other, new randomised clinical trials might have been published since the last published systematic reviews, and on-going trials have been identified on ClinicalTrials.gov. These trials may contribute important information about the use of melatonin in children with neurodevelopmental disorders, including adverse effects. Therefore, there is a need for a systematic review to shed light on this important topic and to assess whether the beneficial effects outweigh any harmful effects. Our systematic review will take risks of systematic errors (‘bias’), risks of random errors (‘play of chance’) and the certainty of the evidence into consideration when assessing the effects of melatonin for sleep disorders in children with neurodevelopmental disorders.

METHODS AND ANALYSIS
The present protocol has been registered in the PROSPERO database and is reported according to the guidance suggested in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P).
statement (please find the checklist in online supplementary material 1).35,36

Criteria for considering studies for this review

Types of studies
We will include randomised clinical trials irrespective of trial design (including crossover trials), setting, publication status, publication year and language. We will use online translation services to translate foreign abstracts and reach out to our international colleagues (who will be thanked in the acknowledgements) for help with data extraction of relevant trials. We will not include quasi-randomised trials, cluster-randomised trials or observational studies.

Types of participants
We will include trials randomising children and adolescents (below 18 years of age) with neurodevelopmental disorders, such as cerebral palsy, epilepsy, Angelman syndrome, Down’s syndrome, Fragile X syndrome, Prader-Willi syndrome, Rett syndrome, Smith-Magenis syndrome, Williams syndrome, non-specific intellectual disability, autism spectrum disorder, ADHD and ADD.12 Trials will be included if the disorders of the participants are diagnosed by standardised diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders37 or International Classification of Diseases38 or where the diagnosis or designation of neurodevelopmental disorder is made by a clinician. The participants also need to have a diagnosis of any type of sleep disorder (as defined by trialists), such as insomnia disorder, hypersomnia, narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorders, REM sleep arousal disorder, non-REM sleep arousal disorder, and nightmare disorders.

We will include participants irrespective of sex, comorbidities, demographic factors, the stage of their condition and the care setting. If a trial reports data where only a subset of participants is eligible (eg, a combination of children and adults), we will only include data from those participants that fulfill the inclusion criteria, and we will therefore require subset data for the specific group to be available.

Types of interventions
We will include trials where participants in the experimental group are given melatonin at any dose, form (eg, tablet, capsules, gummies, liquids), duration of administration, type of administration (eg, oral), timing of administration and setting. We will include trials where participants receive a co-intervention (eg, pharmacological interventions, such as methylphenidate, or non-pharmacological interventions, such as exercise), providing it is delivered equally (in any aspect, eg, same dose, equal subset of population receiving co-intervention) in the experimental group and the control group.

Comparators
As control intervention we will accept placebo or ‘no intervention’.

Types of outcome measures

Primary outcomes
1. Total sleep time (in minutes using any type of measurement, eg, polysomnography, actigraphy, self-report or parent-report).
2. Adverse effects
   a. The proportion of participants with one or more serious adverse events. We will use the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use—Good Clinical Practice (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation, resulted in persistent or significant disability or jeopardised the participant.39 If the trialists do not use the ICH-GCP definition, we will include the data if the trialists use the term ‘serious adverse event’. If the trialists do not use the ICH-GCP definition nor use the term serious adverse event, then we will also include the data provided the event clearly fulfils the ICH-GCP definition for a serious adverse event. We will also analyse each type of serious adverse event separately.
   b. The proportion of participants with one or more non-serious adverse events (any adverse event not classified as serious). We will also analyse each type of adverse event separately.

Secondary outcomes
1. Quality of life of the child (any valid continuous scale, eg, Child Quality of Life Questionnaire).40
2. Quality of life of the parents/caregivers (any valid continuous scale, eg, 36-Item Short Form Survey (SF-36)).41
3. Sleep onset latency (in minutes using any type of measurement, eg, polysomnography, actigraphy, self-report or parent-report).

Exploratory outcomes
1. Quality of sleep (any valid continuous scale), such as the Pittsburgh Sleep Quality Index.42
2. Delayed puberty or any reports of hormonal changes.
3. Any continuous scale assessing adverse effects (eg, Paediatric Adverse Event Rating Scale).43

Timing of outcome assessment
We will include outcome data recorded at the end of the treatment period primarily and at maximum follow-up secondarily.

Search methods for identification of studies

Electronic searches
We will search the following:
► Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in The Cochrane Library.
► MEDLINE Ovid (1946 onwards).
► Embase Ovid (1974 onwards).
Discussion, or, if required, they will consult with a third
review authors will resolve any disagreement through
reasons for exclusion of the ineligible trials. The two
independently screen the full text to identify and record
next phase. We will retrieve all relevant full-
for ineligible results that were submitted
to obtain any additional data, which may not have been
reported sufficiently in the publication. We will extract
the following data:
Methods: trial setting, trial location, trial design, trial
duration, duration of follow-up, date of the trial, esti-
mation of sample size, inclusion criteria and exclusion
criteria.
Participants: number randomised, number analysed
for each outcome, number lost to follow-up, age
(mean and SD), sex ratio and diagnostic criteria.
Interventions: type, dose, timing and duration of
intervention.
Control: type, dose, timing and duration of
comparison.
Co-intervention: type, dose, timing and duration of
co-interventions.
Outcomes: primary, secondary and exploratory
outcomes at the reported time points.
Notes: trial funding and conflicts of interest of the
trial authors.

One review author will transfer the data to Stata. We will
double-check the data by comparing the data presented
in the review to the data extraction form.

Assessment of risk of bias in included studies
Our bias risk assessment will be based on the Cochrane
Risk of Bias tool—version 2 (RoB 2) as recommended in
the Cochrane Handbook of Systematic Reviews of Inter-
ventions. We will evaluate the methodology in respect of
the following bias domains:

- Bias arising from the randomisation process.
- Bias due to deviations from the intended interven-
tions (effect of assignment to intervention).
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias in selection of the reported result.

Review authors in pairs will independently assess the
risk of bias using a template (available at https://www.
riskofbias.info/). Disagreements will be resolved through
internal discussion or, if required, by discussion with a
third author (JCJ). We will use the signalling questions in
the RoB 2 tool to rate each domain at either ‘low risk of
bias’, ‘some concerns’ or ‘high risk of bias’. We will assess
domains of risk of bias for each outcome in each trial.
The overall risk of bias of a result will be judged to be
low if all domains are assessed at low risk of bias. If one
or more domains are assessed at either some concerns or
high risk of bias, the overall risk of bias will be assessed
at high. We will assess the risk of bias for outcomes
of the included trials presented in the ‘Summary of find-
ings’ table (primary and secondary outcomes at end of
treatment). The risk of bias assessments will be illustrated
in a table (using https://www.riskofbias.info/), and the
assessments will be used to conduct subgroup analyses.
The risk of bias assessment will also be used to inform the
Grading of Recommendations, Assessment, Development
and Evaluation (GRADE) and the ‘Summary of find-
ings’ table. For trials using crossover design, only data from the
first period will be assessed.

Open access

- LILACS (Latin American and Caribbean Health
Science Information database; 1982 onwards).
- Science Citation Index Expanded (Web of Science; 1964 onwards).
- Conference Proceedings Citation Index-Science (Web of Science; 1990 onwards).
- PsycINFO (1967 onwards).
- ClinicalTrials.gov.
- International Clinical Trials Registry Platform (ICTRP).

Please see online supplemental material 2 for the
search strategy.

Searching other resources
We will check reference lists of all included trials and any
relevant systematic reviews to identify additional trials. We
will also search for errata and retraction statements for the
included trials. We will search websites of pharmaceutical
companies (eg, Natrol, Neurim Pharmaceuticals, Takeda
Pharma), websites of US Food and Drug Administration
(FDA) and European Medicines Agency (EMA) to iden-
tify relevant trials. We will request FDA, EMA and national
medicines agencies to provide all publicly releasable
information about relevant studies that were submitted
for marketing approval, including clinical study reports.
We will contact authors of eligible trials and other experts
to identify any relevant trials (published or unpublished).

Data collection and analysis
We will perform and report the review based on the recom-
mendations in the Cochrane Handbook for Systematic
Reviews of Interventions. Analyses will be performed
using Stata V.17 and Trial Sequential Analysis.

Selection of studies
Two review authors will independently screen titles and
abstracts using Covidence. We will mark articles that
clearly do not meet the eligibility criteria as excludes,
while potentially eligible articles will go through to the
next phase. We will retrieve all relevant full-text study
reports/publications, and two review authors will inde-
pendently screen the full text to identify and record
reasons for exclusion of the ineligible trials. The two
review authors will resolve any disagreement through
discussion, or, if required, they will consult with a third
author (JCJ). We will select the selection process of the
trials in a PRISMA flow diagram. If multiple reports
are available for a single trial, all reports will be grouped
under a single reference ID.

Data extraction and management
Review authors in pairs will independently extract
data from the included trials using a pilot tested data
extraction form. Disagreements will be resolved through
internal discussion or, if required, by discussion with a
third author (JCJ). The two review authors will assess all
publications of a trial together to evaluate all available
data simultaneously. We will contact trial authors by email
to obtain any additional data, which may not have been
Measures of treatment effect

Continuous outcomes
We will calculate mean differences (MDs) and consider calculating standardised mean differences (SMDs) with 95% CIs for continuous outcomes. We will enter data presented as a scale with a consistent direction of effect. We will primarily analyse scores assessed at single time points. If only changes from baseline scores are reported, we will analyse the results together with follow-up scores for MD (not for SMD). If SDs are not reported, we will calculate the SDs using trial data, if possible, or request such data from the authors.

Dichotomous outcomes
We will calculate risk ratios with 95% CIs for dichotomous outcomes.

Unit of analysis issues
We will only include randomised clinical trials. Trials using a crossover design will be treated as parallel trials, since only data from the first period will be included. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. For trials with multiple relevant experimental or control groups, we will combine the groups as appropriate.

Dealing with missing data
We will, as the first option, contact all trial authors to obtain information on missing data (ie, for data extraction and for assessment of risk of bias, as specified above). We will use intention-to-treat data if provided by the trialists.

Dichotomous outcomes
We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analyses (see below), we will impute data.

Continuous outcomes
We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis (see below) for continuous outcomes, we will impute data.

Assessment of heterogeneity
We will investigate forest plots to visually assess for signs of heterogeneity. We will also estimate the presence of statistical heterogeneity by a χ² test (threshold p<0.05) and measure the quantities of heterogeneity by the I² statistic. We will investigate possible heterogeneity through subgroup analyses. We may ultimately decide that a meta-analysis should be avoided. We will interpret I² heterogeneity as suggested by the Cochrane Handbook for Systematic Reviews of Interventions. If we identify substantial heterogeneity (I²>50%), we will report it, and explore the possible causes by prespecified subgroup analyses. We will carefully investigate trial characteristics and report if we find unexpected heterogeneity due to clinical or methodological factors. Ultimately it will be decided if meta-analysis should be avoided.

Assessment of reporting biases
We will use funnel plots to assess reporting bias if 10 or more trials are included in an outcome. We will visually inspect funnel plots to assess the risk of small trial effects that could potentially reflect publication bias. We are aware of the limitations of a funnel plot (ie, a funnel plot assesses bias due to small sample size). From this information, we will assess possible risk of publication bias. For dichotomous outcomes, we will test asymmetry with the Harbord test if I² is <0.1 and with the Rücker test if I² is >0.1. For continuous outcomes, we will use the regression asymmetry test and the adjusted rank correlation.

Data synthesis
Meta-analysis
We will undertake this meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions, and our eight-step procedure suggested by Jakobsen et al. We will assess our intervention effects with both random-effects meta-analyses (Hartung-Knapp-Sidik-Jonkman) and fixed-effect meta-analyses (Mantel-Haenszel for dichotomous outcomes and inverse variance for continuous outcomes), and report both meta-analysis results. We will primarily report the most conservative result (widest CI and highest p value), and report the less conservative result as a sensitivity analysis. As two primary outcomes are specified, we will consider a p value of 0.025 or less as the threshold for statistical significance for all outcomes. Our primary analyses will include all trials. Where data are only available from one trial, we will use Fisher’s exact test for dichotomous data and Student’s t-test for continuous data.

Trial Sequential Analysis
Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We wish to control for the risks of type I and type II errors. We will therefore perform Trial Sequential Analysis on all outcomes, in order to calculate the required information size (ie, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve’s breach of relevant trial sequential monitoring boundaries. A more detailed description of Trial Sequential Analysis can be found in the manual and at www.ctu.dk/tsa/. For dichotomous outcomes, we will estimate the required information size based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction or a relative risk increase of 25%, an alpha of 2.5% for all our outcomes, a beta of 10% and the observed diversity as suggested by the trials in the meta-analysis. For continuous outcomes, we will use the observed SD in the control group, a mean difference of 30 min when assessing total sleep time; otherwise, a mean difference of the observed SD/2; an alpha of
2.5% for all outcomes, a beta of 10% and the observed diversity of the trials in the meta-analysis. We will only use the diversity-adjusted required information size (DARIS) for random-effects Trial Sequential Analyses.

**Subgroup analysis and investigation of heterogeneity**

We will perform the following subgroup analyses on the primary outcomes:

1. **Type of neurodevelopmental disorder**: this subgroup analysis will assess whether the effects of melatonin are different depending on the neurodevelopmental disorder of the child.
2. **Age (below 12 years compared with above 12 years and preschool-age children compared with school-age children (as defined by trialists))**: this will assess whether the effects of melatonin vary depending on the age of the participants.
3. **Type of comparator (placebo or no intervention)**: this subgroup analysis will assess whether the effects of melatonin vary depending on the comparator.
4. **Timing of the melatonin administration**: if data are available, we will use the following comparisons: <2 hours before bedtime, 2–4 hours before bedtime or 4–8 hours before bedtime. If not, we will use definitions by trialists. This subgroup analysis is relevant, because the timing of administration may affect the outcomes.
5. **Formulation of medication**: this subgroup analysis will assess whether the effects of melatonin vary depending on the formulation of melatonin.
6. **Type of sleep disorder**: this subgroup analysis will assess whether the effects of melatonin vary depending on the type of sleep disorder.
7. **Trials at high risk of bias compared with trials at low risk of bias**: this subgroup analysis will assess whether the effects of melatonin vary depending on the risk of bias of the included trials.
8. **Duration of trials**: this subgroup analysis will assess whether the effects of melatonin vary depending on the duration of the included trials.

Post-hoc subgroup analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results. We will disclose any new subgroup analyses not reported in this protocol in the ‘Differences between protocol and review’ section of the systematic review.

**Sensitivity analysis**

To assess the potential impact of the missing data, we will perform the two following sensitivity analyses on the primary outcomes:

- **‘Best-worst-case’ scenario**: we will assume that all participants lost to follow-up in the experimental group had beneficial outcomes (no serious adverse events/improved quality of sleep defined as the group mean plus two SDs). We will accordingly assume that all participants lost to follow-up in the control group had poor outcomes (serious adverse events/deteriorated quality of sleep defined as the group mean plus two SDs).

We will present the results of both scenarios in our review.

We will assess the potential impact of missing SDs for quality of sleep as follows: when SDs are missing, and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials. We will present results of this scenario in our review.

**Summary of findings and assessment of the certainty of the evidence**

Review authors in pairs will use GRADE to assess the certainty of the body of evidence associated with each of the primary and secondary outcomes at the end of treatment in our review. We will construct ‘Summary of findings’ tables using the GRADEpro GDT. The GRADE approach appraises the certainty of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. We will assess the GRADE levels of evidence as either high, moderate, low or very low certainty on the following quality measures: risk of bias (the overall risk of bias will be used for each outcome), directness of the evidence, heterogeneity of the data, precision of effect estimates (assessed by Trial Sequential Analysis) and risk of publication bias. We will downgrade the evidence by one or two levels due to serious or very serious issues. We will downgrade imprecision in GRADE by two levels if the accrued number of participants is below 50% of the DARIS, and one level if between 50% and 100% of DARIS. We will not downgrade if the cumulative Z-curve crosses the monitoring boundaries for benefit, harm or futility, or DARIS is reached. Two review authors will assess the certainty of evidence independently and decide on downgrading. If no agreement can be reached, a third review author (JCJ) will resolve the discussion. We will justify all decisions to downgrade the certainty of evidence using footnotes, and we will make comments to aid the reader’s understanding of the review where necessary. The ‘Summary of findings’ table will also report the anticipated absolute effects, relative effects, number of participants, type of participants and setting.

**Differences between the protocol and the review**

We will conduct the review according to this published protocol and report any deviations from it in the
future research and clinical practice.

**Patient and public involvement**

None.

**Ethics and dissemination**

Ethical approval was not required for this protocol and systematic review. The results of the systematic review will be published in a peer-reviewed journal to help inform future research and clinical practice.

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