Dietary supplements for aggressive behavior: studies in people with intellectual disability

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Chapter 1

GENERAL INTRODUCTION

This dissertation investigates to what extent dietary supplements can be implemented in practice as an intervention to reduce aggressive behavior in people with intellectual disability (ID). The first paragraph of this Chapter starts with general information about people with ID. The second paragraph deals with the problem of aggressive behavior in people with ID and is followed by a paragraph on treatment of this behavior. Because treatment with dietary supplements interacts with nutrition, diet quality in people with ID is discussed in paragraph four. Paragraph five explains the rationale for using dietary supplements to reduce aggressive behavior. Finally, paragraph six provides an overview of the content of the Chapters of this thesis.

People with intellectual disability

Intellectual disability is defined by both impaired intellectual functioning and a deficiency in one or more areas of adaptive behavior (APA, 2013). Adaptive behavior refers to the social, practical and conceptual skills in people's daily lives (Tassé et al., 2012). The impairments must be present before the age of 23 to differentiate ID from, for example, dementia. People with ID are characterized by a relatively high prevalence of psychological problems, health problems, and challenging behavior (Bowring, Painter, & Hastings, 2019; Matson & Cervantes, 2013). The cause of the ID can be genetically determined, as for example in the case of trisomy-21 in people with Down syndrome. However, ID can also be the result of environmental factors that disrupt an optimal development of the central nervous system (CNS), such as through a viral infection or oxygen deficiency in utero. In many cases, the cause of ID is unknown (Simpson, Mizen, & Cooper, 2016).

When diagnosing an ID, both intelligence quotient (IQ) and adaptive behavior are assessed (Tassé, Luckasson, & Schalock, 2016). Scales used for the assessment of IQ are for example Wechsler Adult Intelligence Scale (WAIS-IV; (Wechsler, 2012), Wechsler Intelligence Scale for Children V (WISC-V; (Wechsler, 2017), and the Wechsler Non-Verbal (WNV; (Wechsler & Naglieri, 2008). Also, for the assessment of adaptive behavior different scales are used, for example the Adaptive Behavior Assessment System-3 (ABAS-3; (du Preez, 2017), the Vineland-3 (Sparrow, Cicchetti, & Saulnier, 2016), and the ADaptive Ability Performance Test (ADAPT; (Jonker, Didden, Goedhard, Korzilius, & Nijman, 2021). Both the IQ tests and the adaptive behavior tests use a cut-off value of

approximately 2 standard deviations below the mean of the general population (IQ 70-75) (Boat, Wu, National Academies of Sciences, & Medicine, 2015).

Four different levels of severity of ID are distinguished within the group of people with ID (Boat et al., 2015). In the DSM-5, the severity categories are defined by a person's adaptive functioning, while in the DSM-IV IQ scores were dominant (Table 1.1). The categories are: profound ID, severe ID, moderate ID, and mild ID (MID). There are also people with an IQ between 69 and 85, a significant number of whom run into problems due to inadequate adaptive skills. In the Netherlands, they can receive comparable support from care organizations as people with MID (Nouwens, Lucas, Smulders, Embregts, & van Nieuwenhuizen, 2017). These people are not considered as having ID, but their level of functioning can be classified as borderline intellectual functioning (BIF). The prevalence of people with ID within the general population worldwide is estimated to be around 1-2%, but depends on the methods and study samples used (Maulik, Mascarenhas, Mathers, Dua, & Saxena, 2011; McConkey, Craig, & Kelly, 2019). When people with BIF are also included the prevalence is much higher. In the Netherlands, the prevalence of the group of people with MID/BIF was an estimated 6.4% (4.8-8.3%) (Woittiez, Eggink, & Ras, 2019). Table 1.1 shows the distribution of severity levels of ID relative to the total number of people with an ID.

Table 1.1 Severity categories of people with ID as defined by DSM-IV

Severity Category	Distribution of Cases by Severity	DSM-IV Criteria (IQ categories)
Mild	85%	Approximate IQ range 50–69
Moderate	10%	Approximate IQ range 36–49
Severe	3.5%	Approximate IQ range 20–35
Profound	1.5%	IQ < 20

Note. Adapted from "Clinical characteristics of intellectual disabilities: In Mental disorders and disabilities among low-income children," by T. F. Boat, J. T. Wu, E. National Academies of Sciences, Engineering, and Medicine, 2015, p.171 National Academies Press (US).

Aggressive behavior in people with ID

Aggressive behavior exhibited by people with ID is a serious problem. It causes suffering in both the client and his or her environment and may contribute to the use of restrictive

measures and may affect the possibility of clients to live independently. It also contributes to the workload and burn-out of healthcare professionals. Staff members working in the care for people with ID have a high risk of being a victim of clients' aggression. The annual prevalence of staff workers encountering physical aggression at least once is 64% compared to an average of 38% across all healthcare domains (PGGM&CO, 2021).

Table 1.2 Examples of different types of aggressive behavior measured with the MOAS

Type of Aggressive Behavior	**Severity**	**Example of Behavior**
Verbal Aggression	Mild	Shouts angrily, curses mildly, or makes personal insults
	Moderate	Curses viciously, is severely insulting, has temper outbursts
	Severe	Impulsively threatens violence
	Extreme	Threatens violence repeatedly or deliberately
Aggression Against Property	Mild	Slams door, rips clothing, urinates on floor
	Moderate	Throws objects down, kicks furniture, defaces walls
	Severe	Breaks objects, smashes windows
	Extreme	Sets fires, throws objects dangerously
Physical Aggression	Mild	Makes menacing gestures, swings at people, grabs at clothing
	Moderate	Strikes, pushes, scratches, pulls hair of others (without injury
	Severe	Attacks others, causing mild injury (bruises, sprain, welts, etc.)
	Extreme	Attacks others, causing serious injury
Autoaggression	Mild	Picks or scratches skin, pulls hair out, hits self (without injury)
	Moderate	Bangs head, hits fists into walls, throws self onto floor
	Severe	Inflicts minor cuts, bruises, burns, or welts on self
	Extreme	Inflicts major injury on self or makes a suicide attempt

Aggression in people with an ID falls within the overarching concept of challenging behavior, which includes stereotypic and self-harm in addition to aggression. There is no uniform definition for aggression in people with, or without ID. Without a uniform operational definition of aggressive behavior, a wide variety of prevalence rates is to be expected. The variety is further increased by different study samples and settings in which the studies were conducted. The prevalence of aggressive behavior is estimated to lie between 9% and 50% or even higher in forensic treatment facilities (Didden et al., 2016). The prevalence rate varies with age and increases steadily from childhood until adulthood around age 45 (Davies & Oliver, 2013).

Various observer-reported instruments are used to measure aggressive behavior in people with ID. Often used examples include the Modified Overt Aggression Scale (MOAS;

(Oliver, Crawford, Rao, Reece, & Tyrer, 2007), and the Social Dysfunction and Aggression Scale (SDAS; (Wistedt et al., 1990). The MOAS, on the one hand, records the number of aggression incidents and their severity over a certain period, for example a day or a week (Table 1.2). The SDAS, on the other hand, records a score for certain forms of aggressive behavior over a certain period. There are also scales in which aggressive behavior is part of a broader spectrum of behavior, such as the Aberrant Behavior Checklist (ABC; (Aman & Singh, 1994), the Adult Behavior Checklist (ABCL; (Achenbach, Dumenci, & Rescorla, 2003), and the Behavior Problems Inventory (BPI; (Rojahn, Matson, Lott, Esbensen, & Smalls, 2001). In the latter checklists, compared to the first, aggressive behavior is described in less detail in terms of type and severity.

Aggressive behavior usually does not have a single cause, but results from a combination of factors that together determine the risk of occurrence of the behavior. Poor emotion regulation and inefficient coping mechanisms are examples of psychological determinants. Other risk factors for aggression in people with ID can be client-specific, such as certain syndromes (Arron, Oliver, Moss, Berg, & Burbidge, 2011), a more severe level of ID, and mental health and medical problems (Crocker, Prokić, Morin, & Reyes, 2014). Some studies find that men with ID show more aggression than women, but the results are inconclusive and vary by study and by type of aggression (Crocker et al., 2006). Environmental factors can be related to aggression, such as the quality of the interaction between client and caretaker (van den Bogaard, Nijman, Palmstierna, & Embregts, 2017). There is also a negative association between the living climate and the level of aggression in the group (Neimeijer, Delforterie, Roest, Van der Helm, & Didden, 2020).

Studies have been done on the neurobiology of aggression and although neurotransmitters such as serotonin, dopamine and γ-aminobutric acid play multiple roles in the phenomenon of aggression, the causality is less clear-cut than initially thought (Willner, 2015). Because these neurotransmitters can have both activating and inhibitory functions in different brain regions involved in aggression, there is no simple causal relationship between the physiological availability of neurotransmitters and aggressive behavior (Takahashi, Quadros, de Almeida, & Miczek, 2010).

Treatment of aggressive behavior

Various approaches have been studied for the treatment of aggressive behavior in people with ID, which can be divided into four categories: 1) behavioral therapies, 2) cognitive behavioral therapies (CBT), 3) mindfulness-based techniques, and 4) psychotropic

medication. These approaches will be summarized below, with a special focus on psychotropic medication because it resembles treatment with supplements more than the other therapies.

Behavioral therapy interventions are based on Skinner's work and assume that aggressive behavior is learned and/or maintained through operant conditioning (McLeod, 2015). The intervention can consist of learning adaptive behaviors, changing the environment, changing reinforcement patterns of behavior and breaking routines. In behavioral therapies two steps are distinguished. After functional behavioral assessment (step 1) a behavioral intervention is chosen aimed at differential reinforcement or extinction of a certain target behavior (step 2) (Didden et al., 2016). A well-known shortcoming of such an approach is that generalization across settings of treatment results often does not occur and needs to be explicitly trained. Much research has been done – especially in individuals with more severe levels of ID – on behavioral interventions for aggressive behavior in people with ID and multiple systematic reviews and meta-analyses support their effectiveness (Didden et al., 2016).

Anger management Treatment (AMT) is an example of CBT that is often used in case of aggressive behavior. It is a multi-component intervention with the aim of learning to regulate anger in real life situations (Didden et al., 2016). It consists of learning to identify and control increased arousal and understand own emotions and those of others. Newly learned skills are practiced with anger-provoking stimuli in controlled environments (Didden, Nijman, Delforterie, & Keulen-De Vos, 2019). To increase effectiveness, standard CBT programs are adapted to people with ID through, among other things, simple language, using role plays, and involving significant others (Lindsay, 2009). CBT/AMT has many components and for many individuals with mild ID the approach may be too difficult. It is not yet known which parts of CBT/AMT have the most effect on aggressive behavior although it is generally assumed that role-play is more effective than cognitive elements (Didden et al., 2019).

Mindfulness-based therapies have also been used for treating aggressive behavior. Through mindful exercises, participants learn to focus their attention and reduce negative emotions and emotional reactivity (Currie, McKenzie, & Noone, 2019). An example of a mindfulness-based treatment is “Meditation on the soles of the feet”, in which a person practices with recognizing precursors to aggressive behavior and focusing his or her attention to a neutral point in the body (Singh et al., 2012). Systematic

reviews show promising results of this approach for the treatment of aggression, but both the number and quality of the studies are not yet sufficient to draw firm conclusions about its effectiveness (Patterson, Williams, & Jones, 2019).

The use of psychotropic drugs for aggression is widespread but not without controversy. Approximately 40% of people with ID who are living in a residential facility use antipsychotics, of whom only a part have an indication for these prescriptions (Koch, Dobrindt, & Schützwohl, 2021; Lunsky et al., 2017). The widespread use of antipsychotics is not without risks as there is evidence that the side effects can lower quality of life, cause serious health risks and side effects, and shorten lifespan (Espadas et al., 2020; Scheifes et al., 2016; Sheehan et al., 2017; Tyrer, Cooper, & Hassiotis, 2014). The evidence that antipsychotics are effective in treating aggressive behavior among people with ID is not strong and leans on open label trials and industry conducted RCTs with relatively small sample sizes (Cohen et al., 2013; Deb, 2016; Deb et al., 2014). The reviews and meta-analyses are not unambiguous about the direction of the effect (Brylewski & Duggan, 2001; Cohen et al., 2013; Deb et al., 2014). Good quality RCTs need to be conducted to justify its widespread use (Deutsch & Burket, 2021). Also, some studies show that tapering off antipsychotics yields health benefits and improves the quality of life of people with ID (Ramerman, Hoekstra, & de Kuijper, 2019), and does not necessarily lead to more aggression (Kuijper, Evenhuis, Minderaa, & Hoekstra, 2014; Ramerman, Kuijper, et al., 2019). The abundant use of antipsychotics among people with ID has led to the development of protocols and guidelines for a more responsible prescription. Only after psychological interventions have remained unsuccessful antipsychotics may be prescribed. In addition, there must be a clear indication, and the intervention must be regularly evaluated (Deb et al., 2009; Deutsch & Burket, 2021; Embregts et al., 2019; NICE, 2015). Despite clear protocols, the use of psychotropic drugs as an off-label medication proves difficult to control (Henderson et al., 2020). The slight decline in antipsychotic prescribing in the second decade of this century was offset by an increase in the prescribing of other psychotropic drugs, such as antidepressants, hypnotics, and anxiolytics (Henderson et al., 2020). The search for an alternative to excessive off-label prescribing of psychotropic drugs for aggressive behavior prompted this study. From the above, we can conclude that several treatment options for aggression in people with ID have been developed. But, all current treatments have their own limitations and evidence

is equivocal in people with ID. Additional therapies that are easy to implement and have few side effects remain necessary.

Nutritional status among people with ID

The nutritional status influences the composition and condition of the body and is determined by the bioavailability of nutrients on the one hand and the consumption of nutrients on the other (Kondrup, 2003). In people with ID, a good nutritional status faces multiple threats (Humphries, Traci, & Seekins, 2009; Ptomey & Wittenbrook, 2015). We will briefly discuss three of those threats here: 1) poor diet quality, 2) medication, and 3) genetic polymorphisms (Ames, Elson-Schwab, & Silver, 2002; Boullata & Armenti, 2004; Hamzaid, O'Connor, & Flood, 2019; Hoey et al., 2017). Diet quality is defined as a person's overall dietary pattern. A so-called Western dietary pattern is characterized on the one hand by too much saturated fat, animal proteins and fast carbohydrates, which increases the risk of obesity and a range of health problems. On the other hand, a Western diet is characterized by a relative deficiency of dietary fiber, vitamins, minerals and omega-3 fatty acids (Cena & Calder, 2020; Cordain et al., 2005). A healthy diet is characterized by fresh fruits and vegetables, whole grains, legumes, seeds and nuts and contains relatively little fast carbohydrates such as sugar and little animal-based foods such as processed meat (Cena & Calder, 2020). Unhealthy food is widely available and relatively cheap (Appelhans et al., 2012). The risk of a less healthy diet is related to a low socio-economic status and educational level (Giskes, Turrell, Van Lenthe, Brug, & Mackenbach, 2006; Hiza, Casavale, Guenther, & Davis, 2013). Multiple studies show that the diet quality of people with ID is lower than the standards for optimal nutrition and often lower than that of peers without ID (Ptomey & Wittenbrook, 2015).

In addition to low diet quality, there are lifestyle factors that can threaten nutritional status through a negative effect on the bioavailability of vitamins and minerals. Examples are smoking, drinking alcohol, and using certain medications, which include anticonvulsants and antipsychotics that are widely used by people with ID (van den Berg, van der Gaag, & Hendriks, 2002; Berg, 2004; Boullata & Armenti, 2004). Finally, it is assumed that a relative deficiency of micronutrients can be caused by an increased need, which can be the result of genetic polymorphisms that affect between 1% and 35% of individuals. The abnormalities in the genetic code can lead to the production of malformed enzymes that have a lower binding affinity with their cofactor (often a

vitamin), resulting in a decreased biological activity of the enzyme. A higher blood level of the cofactor involved can improve this biological activity (Ames et al., 2002).

We may conclude that there are several risks to a healthy nutritional status of people with ID. Firstly, there is a risk that the client with ID – especially clients with milder levels of ID – makes unhealthy food choices. Secondly, there may be problems swallowing and digesting healthy foods, which often occurs in people with more severe ID. Thirdly, there may be an increased need for micronutrients due to lifestyle factors, medication and genetic abnormalities.

Effect of micro-nutrients on behavior

Full-blown physical deficiency diseases due to micronutrient deficiency in the diet are rare in Western societies and are mostly seen as comorbidities of serious disease or alcohol dependence. More common is a chronic latent deficient intake of vitamins, minerals and omega-3 fatty acids, which is associated with a Western diet (Myles, 2014; Troesch, Hoeft, McBurney, Eggersdorfer, & Weber, 2012). These mild chronic deficiencies can limit optimal CNS function and are associated with a risk of disruptive behaviors (Benton, 2007; Jackson, 2016).

Vitamins, minerals and omega-3 fatty acids are important for the functioning of the CNS because of the many roles they play in the physiological processes of nerve cells. As was described in 1.2, there is no simple causality between physiological availability of neurotransmitters and aggression. Because of the complex nature of the interactions between environmental factors and the CNS and the many feedback mechanisms that characterize neurophysiological processes, the relations are less straightforward than had been expected a few decades ago. There are several hypotheses about pathways by which micronutrients affect the CNS and may influence human behavior (Huskisson, Maggini, & Ruf, 2007; Parletta, Milte, & Meyer, 2013). Here, we briefly explain three possible routes: 1) neurotransmitter function, 2) CNS energy supply, and 3) neuroprotection.

1) Neurotransmitter function

A pathway by which micronutrient bioavailability affects the CNS is that it acts as a coenzyme in the synthesis of various neurotransmitters. The B-vitamins, such as B1 (thiamine), B2 (riboflavin), B6 (pyridoxine, pyridoxal and pyridoxamine), folic acid (vitamin B11), and B12 (cobalamin) are involved as coenzymes in the metabolism of several neurotransmitters, including serotonin, dopamine, noradrenaline, and GABA.

Brain-specific symptoms of deficiency of B-vitamins include irritability, emotional disturbances, cognitive impairment, depression, psychotic symptoms and aggression (Kennedy, 2016). Vitamin D is lipophilic and has characteristics of a steroid hormone. It plays a role in the development of the CNS and the proper functioning of neurotransmitters. Low vitamin D status has been linked to a number of mental illnesses, such as schizophrenia, depression and cognitive decline (Eyles, Burne, & McGrath, 2013). Indirectly, also Omega-3 fatty acids (FA) have an effect on the functioning of neurotransmitters. The fluidity of the neuron cell membrane is increased by the presence of docosahexaenoic acid (DHA), which has a beneficial effect on the functioning of the membrane proteins such as the receptors of the monoaminergic neurotransmitters (Parletta et al., 2013).

2) CNS energy supply

The CNS needs much energy to function optimally that is about 20% of the total body requirement at rest. For special tasks, the need can increase even further. For example, self-control is linked to reduced aggressive behavior. There is evidence that self-control relies on an optimal energy management of the CNS (Gailliot et al., 2007). B vitamins are involved in the process of catabolic energy production via direct roles in the citric acid cycle and the formation of the energy carrier adenosine triphosphate (ATP) (Kennedy, 2016). Also, a number of minerals like chromium, iron, magnesium, manganese and zinc are involved in the energy metabolism of the CNS (Huskisson et al., 2007).

3) Neuroprotection

There are multiple ways in which micronutrients are involved in protecting nerve cells in the performance of their function. The below examples do not provide a comprehensive overview but illustrate the roles that the different micronutrients have in the protection of the CNS. Elevated homocysteine levels in the blood are associated with neuro damage and an increased risk of depression, schizophrenia and a decline in cognitive functions. Sufficient bioavailability of vitamin B6, folic acid and vitamin B12 as well as all other B-vitamins are indispensable for the conversion of homocysteine into methionine (Kennedy, 2016). As an end-product of the methionine cycle, glutathione is produced, which is the basis of a potent antioxidant in the CNS, a prophylaxis against oxidative damage of the CNS (Kennedy, 2016). Vitamins C, E and selenium are also antioxidants and have neuroprotective properties (Kaplan, Crawford, Field, & Simpson, 2007). Adequate bioavailability of omega-3 FA has a neuroprotective effect in another

way. Chronic low-grade inflammatory processes may contribute to neurodegeneration. Omega-3 FA have anti-inflammatory properties through the production of leukotrienes (Parletta et al., 2013). Other micronutrients such as vitamin A, B6, B11, B12, C, D, copper, iron, selenium and zinc play synergistic roles in the proper functioning of the immune system (Messina, Lampe, Birt, & Appel, 2001).

As described above, there are several ways in which vitamins, minerals, and omega-3 FA support the CNS. A reductionist view of the effect of an isolated nutrient on a single process has important limitations (Messina et al., 2001). It is not one micronutrient that facilitates a particular process, but it is a chain of reactions in which many micronutrients play a role in mutual cohesion (Kennedy, 2016). That is why we are interested in the effect of a broad spectrum of micronutrients and omega-3 FA on aggressive behavior in the present thesis.

Research among prisoners and youngsters with mental health problems shows that dietary supplements may reduce aggressive behavior. Since the 1990s, studies have shown effectiveness of dietary supplements on behavior of young male inmates (Gesch, Hammond, Hampson, Eves, & Crowder, 2002; Schoenthaler et al., 1997; Schoenthaler, Gast, Giltay, & Amos, 2021; Zaalberg, Nijman, Bulten, Stroosma, & Van Der Staak, 2010). The beneficial effects were mainly seen in the reduction of rule violations as the primary outcome measure. There was no effect on the self-report scales for aggression and anger, used as a secondary outcome measure. Furthermore, research into the effectiveness of vitamins on behavior has been conducted among other target groups such as (school) children and university students and people with mental health problems (Adams et al., 2018; Long & Benton, 2013; Raine et al., 2016; Rucklidge, Eggleston, Johnstone, Darling, & Frampton, 2018; Schoenthaler & Bier, 2000). In addition to positive effects on the number of aggression incidents, there were also studies with equivocal results (e.g., Tammam, Steinsaltz, Bester, Semb-Andenaes, & Stein, 2016), and a study showing no effect (De Bles, 2022).

Aim and outline of this thesis

Aggressive behavior of people with ID is a major and – in many cases – persistent problem. Several psychological therapies are currently being used such as behavioral therapy, anger management, and mindfulness-based therapy. Also, off-label antipsychotics are widely used with potentially serious side effects and limited evidence of effectiveness. Despite these therapies, there remains a need for affordable, effective,

and low-impact therapies for aggression in individuals with ID. Research into the effect of dietary supplements on aggressive behavior among prison inmates shows promising results. Due to the low diet quality in people with ID, we expect that dietary supplements may be effective. The primary aim of this thesis is to investigate whether an intervention with dietary supplements can be used in clinical practice to reduce aggressive behavior in people with ID.

In Chapter 2, we conduct a cross-sectional study on the quality of nutrition in people with ID. We use the "Eetscore" food frequency questionnaire to measure nutritional quality and use participants from the "Eet, weet en meet studie" as control group. We hypothesize that people without ID have a higher diet quality than people with ID.

Next, in Chapter 3, we conduct a qualitative study into the acceptability of an intervention with dietary supplements among clients with ID, client representatives and professionals of a facility for ID-care. Using focus groups, we collect data and use constant comparison analysis based on grounded theory.

In Chapter 4, with access to data from a study conducted in the 1990s, we investigate the effect of multivitamin and mineral supplementation on serious rule-breaking behavior of inmates in correctional facilities in California in a three arm RCT. The placebo arm is compared with a dose of approximately 100% and 300% ADH. The primary outcome measure is serious rule-breaking behavior, and the duration of the intervention is 15 weeks.

In Chapter 5, we study the effect of multivitamin-mineral, and omega-3 FA supplementation on aggressive behavior in people with ID. The age of the participants is 12 to 40 years old; they live in a care facility for people with ID or receive day care. It is a triple-blind randomized placebo-controlled pragmatic study, and the aggression incidents are measured daily with the MOAS (see 1.2). The intervention period is 16 weeks, followed by a cross-over of the same duration. We hypothesize that dietary supplements are effective to reduce aggressive behavior.

In Chapter 6, we conduct a systematic review of studies on the effect of vitamins and minerals on aggressive behavior. In addition, we perform a meta-analysis to determine the pooled effect size of these different studies.

In Chapter 7, we focus on the challenges encountered when conducting an intervention study with dietary supplements in vulnerable target groups. We will thereby focus on five main themes: 1) multiple sites study, 2) inclusion of vulnerable participants, 3)

intervention with dietary supplements, 4) behavioral outcomes, and 5) collecting bio samples.

In Chapter 8, finally, we start with a summary of the main findings and continue with a general discussion of the methods and outcomes of the studies included in this thesis and provide recommendations for clinical practice and further research.

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