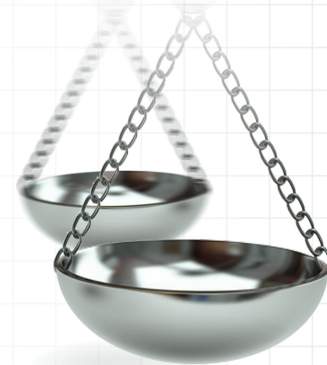




An investigation to choose the proper therapy technique in the management of autism spectrum disorder

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Aim: Autism spectrum disorder is a class of neurological disorders that affect the development of brain functions. This study aims to evaluate, compare and rank the therapy techniques used in the management of autism spectrum disorder using multicriteria decision-making approaches. **Materials & methods:** Fuzzy PROMETHEE and fuzzy TOPSIS approaches were used. Fuzzy PROMETHEE utilizes a pair-wise comparison of alternatives under the fuzzy environment while fuzzy TOPSIS utilizes geometric distance from the positive ideal solution under the fuzzy environment for the evaluation of the effectiveness of the alternatives. The techniques selected for evaluation are applied behavioral analysis, cognitive behavioral therapy, speech therapy and pharmacological therapy such as Risperidone and Aripiprazole. Criteria used in this study include efficacy, cost and side effects, and their weights are assigned based on specific patient conditions. **Results:** The results indicate that applied behavioral analysis, cognitive behavioral therapy and speech therapy are the most preferred techniques, followed by Aripiprazole and Risperidone. **Conclusion:** More criteria could be considered and the weights could be assigned according to the patient profile.

Lay abstract: Autism spectrum disorder is a neurodevelopmental disorder (affecting the development of the brain) that usually presents during childhood. Because autism spectrum disorder has no cure, selecting the best therapy to manage the disorder is important for therapists, parents, health institutions and researchers with an interest in these types of disorders. This study focuses on comparing specific therapy techniques by using multicriteria decision-making methods. The result obtained by a decision-maker is not always the same, as different decision-makers may come up with different solutions depending on things like the cost and how well a therapy works on different aspects of the disorder. The outcome of the study indicates that applied behavioral analysis, cognitive behavioral therapy and speech therapy are preferred treatment alternatives, followed by treatment with Risperidone and Aripiprazole. Further analyses are needed to obtain more accurate patient-specific results that will incorporate specific patient demographics and data, as well as looking at the combination of two or three techniques.

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Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental disorder. The term ASD is used by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) and additional specifiers are used to differentiate patients [1]. Clinical findings in ASD include impairment in social communication and interaction, restrictive interest, repetitive behaviors, sensory abnormalities and intellectual disability. ASD can be co-morbid with other conditions like Attention Deficit and Hyperactivity Disorder, anxiety, depression and epilepsy. The diagnosis of ASD is mainly based on a detailed developmental history and observation of the patient [2].

Future
Medicine

Although the underlying mechanisms and etiology of ASD remain unclear, there are several factors that are demonstrated to increase the risk of ASD. These include advanced paternal age, birth trauma causing hypoxia [3,4], gestational diabetes, maternal obesity, short duration in between pregnancies and valproate usage during pregnancy [3,4]. Environmental risk factors were hypothesized to increase risk via genetic and epigenetic effects like inflammation, hypoxia causing oxidative damage and ischemic process [4]. With increased accessibility and usage of genetic tests more than 100 genes and genomic regions have been associated with ASD [5,6]. In addition, family studies displayed a large genetic contribution with an estimated heritability ranging from approximately 40–90% [7,8].

The Global Burden of Disease Study estimated that 52 million people were living with autism globally in 2010, denoting one in 132 individuals [9]. The Autism and Developmental Disabilities Monitoring Network demonstrated ASD prevalence as 18.5 per 1,000 (one in 54) children aged 8 years, and ASD was 4.3-times as prevalent among boys as among girls [10]. The prevalence of ASD in people with mental disorders was demonstrated to range from 4 to 9.9% [11].

Disability and functioning across the lifespan highly vary among different individuals with ASD with different clinical involvement. A broad variety of functional differences had been demonstrated in respect to disability and exceptionality by Schipper *et al.* [12]. Sixty-five percent of people with ASD had been reported a profound or severe disability at least one of the functioning domains (Australian Bureau of Statistics). Outcomes of individuals with ASD highly vary according to cognitive, linguistic, social and behavioral limitations. It is hard to categorize and evaluate clinical studies collectively as the have different sampling methods, diagnostic criteria and follow-up. In a study with quantifiable criteria of outcomes, among 68 adults with autism with an IQ level of ≥ 50 majority (58%) had poor or very poor outcomes. Intelligence quotient (IQ) seems to be an important prognostic factor for the outcomes [13,14].

As a result of the heterogeneity in reviewing indicators of ASD, lack of biological diagnostic inferences and changing diagnostic criteria, tracking the spread of ASD is one of the unique challenges. Although the initial symptoms appear during the early growth stage, it may be difficult to define these symptoms as being diagnostic indications for ASD until the child has reached the important developmental stages where it is ensured that the child is unable to meet the criteria of social, educational and professional stages. The complex overlap in diagnostic criteria and clinical differences for decision-making in addition to the policy of standards that determine the eligibility for health benefits and educational programs complicate the possibility of identifying ASD as a behavioral or exceptional health diagnosis. There are various dimensions of the disorder like impaired social communication, restrictive interest, repetitive behaviors, sensory abnormalities and intellectual disability. Moreover, co-morbid disorders are demonstrated to be higher when compared with population [15,16]. Linguistic delay, motor problems, epilepsy, sleep disturbances and eating problems are observed in preschool children with autism [17,18]. For school-aged children anxiety, Attention Deficit and Hyperactivity Disorder, obsessive compulsive disorder and disruptive behaviors are observed [19], and for adolescents and adults' depressive symptoms observed more [20].

Treatment of ASD can be broadly divided into behavioral/psychological interventions such as applied behavioral analysis (ABA) and biological interventions such as medication. In addition, treatment can be divided into those that address key underlying symptoms such as applied behavioral analysis (ABA) and those that treat associated features such as mood or aggression.

Most of the current interventions are based on ABA. There is great diversity among different interventions. For example, mode of delivery (parent mediated/therapist implemented), length of training (12-week to 2-year program), intensity (few hours/week to 15 h/week) highly varies. Individual outcomes within same groups also vary. Use of cognitive behavioral therapy (CBT), for instance, demonstrated to be effective in the treatment of anxiety in individuals with autism with sufficient cognitive and language skills [21]. Cognitive impairment and linguistic problems set limitation for CBT.

The medications that are reported to be beneficial for autism are not directly against the autistic domains. The drugs that are approved by the US FDA for the treatment of irritability and agitation (including aggression, self-injury and tantrums) in autism are the neuroleptics Risperidone and Aripiprazole [22–24]. Both of these drugs have side effects like sedation, weight gain and risk of movement disorders [23].

The cost of treatment for autistic patients in the USA reached US\$268 billion in 2015 and is expected to increase to US\$461 billion by 2025 [25]. For a professional, it is important to make the right decision for the benefit of the patients. It is crucial and potentially difficult to choose the best treatment choice. Several parameters underlie the approach taken to the correct treatment and these requirements are not always well described and presented.

Efficiency and side effects are the key criteria for assessment, though other criteria such as cost, safety, treatment time and patient delivery should be taken into account. Well-known models of treatment help health providers choose and have better strategies for treating conditions. An additional advantage of evaluating modes of care is that it helps to speed up patient remission and improve prognostic outcomes.

In the absence of uncertainties, the fuzzy multicriteria decision-making (MCDM) methods applied have become an important method to help professionals compare and make better alternatives. This is a powerful approach to addressing decision-making issues involving the selection and implementation of the system based on a variety of critical criteria for characterizing alternatives [26,27].

The ideal treatment is acknowledged as including features such as having efficiency, a rapid duration of action, safety, an absence of any adverse side effects and comfort. Therefore, it is the task of the clinician to determine the most appropriate option for each individual for maximizing the patient's comfort while minimizing the patient's risks and treatment's possible side effects. To do so, the clinician carries out a preoperative evaluation and assesses all possible factors, including individuals' medical history in a cost-effective manner that might have an impact on the selection process of an optimal treatment technique. This study aims to evaluate, compare and rank the therapy techniques used in the management of ASD using the fuzzy preference ranking organization method for enrichment evaluation (PROMETHEE) and technique for order preference by similarity to ideal solution (TOPSIS) – Multi Criteria Optimization and Compromise Solution, MCDM methods. Applying MCDM methods in evaluating treatment options of ASD, based on the selected criteria and their assigned weights, may contribute to a more accurate decision-making process for the clinicians and result in better management of the disorder.

Specific therapy techniques

The investigation done in this study is to apply MCDM methods to the selecting the 'right' therapy technique in the management of ASD. In order to evaluate the therapy techniques, first, we defined the widely used techniques and extract the important parameters of interest such as efficacy, cost and side effects of each technique. Here, we list and summarize the most common therapy techniques, then, explain the MCDM techniques, and finally show how to apply them.

The plasticity of the brain is highest during childhood and decreases with aging. Based on this, ASD treatments and interventions delivered during preschool ages are considered to have the highest benefit, even though this has not proven empirically. Clinical trials on ASD are inappropriate for a comparison. The main limitations are limited outcome measurements, costs and placebo effects [28].

CBT, for instance, requires trained personnel and is time consuming. It has been demonstrated in adult studies to be better applied to individuals with sufficient cognitive and language skills [21]. Research has indicated that considerable progress in cognitive and language skills in an infant with ASD can be achieved when behavioral therapy is mandated and applied during their preschool years. There is no single optimal treatment for all children with ASD [29]. The goal of treatment in autistic cases is to improve the child's functional abilities, quality of life and provide support to the patient. A major limitation is that behavior is affected by many factors and these need to be considered within the context of the developing child.

The National Institute of Mental Health [30] recommends starting treatment immediately after diagnosis. Early detection and treatment for ASD are important as suitable care can reduce individual impairments while helping them to overcome difficulties by learning new skills and improving most of their strengths. The heterogeneity of ASD and the diversity of therapy options makes it difficult to determine a single and optimal treatment for the condition. The treatment system can include different kinds of behavioral therapy techniques to improve communication and behavior, and sometimes medications may help to manage co-morbid conditions related to ASD. The goal of the treatments is the same for all types of therapeutic techniques, namely to reduce ASD symptoms, improve communication skills and function to be able to provide a better quality of life. Behavioral and social therapy, speech therapy and pharmacological therapy were the therapies of choice in this study.

The selective serotonin reuptake inhibitors (SSRIs) are widely used in the treatment of symptoms related to ASD. In a review evaluating the efficacy and tolerability of three commonly used SSRIs (fluoxetine, fluvoxamine, citalopram) conducted no convincing evidence for the use of them in the treatment of children with ASD. In addition, evidence of them for clinical utility in adults is inadequate [31]. Hence, SSRIs are not considered in this study.

Behavioral & social therapy

Behavioral and speech-language therapy forms the basis of ASD treatment [30]. Behavioral therapy is an effective and safe approach for dealing with children with ASD. However, the high cost of this approach and the need for labor intensity is one of the disadvantages that is difficult to solve in addition to the fact that it includes a variety of methods, which make it more difficult to decide on the optimal method. Nevertheless, behavior therapy remains the most reliable way of developing the skills of autistic children, provided that the time and energy focus is located, whether parent mediated or therapist implemented.

Applied behavioral analysis

This therapy is based on focused theories aimed at developing learning and adapting, based on an organized scientific approach that includes specific intervention goals for positive reinforcement and repetition of learning experiences, where specific methods are used to teach how to play and socialize and enhance self-care and academic skills, and thus reduce problematic behaviors [32]. In the ABA approach, the child's abilities are observed by the therapist as a first step to determine what will benefit the applications that help the patient to move away from repetitive and focused behaviors. ABA is the usual starting point for treating children with severe symptoms to enhance skills and improve social communication. Outcomes depend on several factors. For example, parent-mediated, lower intensity, time-limited interventions may over time have no improved outcome [21].

Cognitive behavioral therapy

CBT is used for children and adolescent with moderate symptoms, especially for the treatment of anxiety in individuals with autism with sufficient cognitive and language skills [22]. This treatment enhances the knowledge of the affected children at the moment they embarked on the habitual behavioral or mental frequent activity. The therapist determines the behavioral stimuli needed by the ASD children in the case in question in order to help them recognize these moments themselves. These behavioral stimuli interfere in cases of severe fear and anxiety to reduce the impact of the stress of the condition on the effectiveness of these children's activities.

Speech therapy

Speech therapy deals with verbal and nonverbal social communication in individuals with ASD. This therapeutic technique aims to help autistic people to communicate in ways that are highly effective and practical; therefore, the help of a speech and language pathologist is critical for taking the treatment to a more efficient level. Nonverbal methods like 'sign language, visual aid systems and picture exchange communication system (PECS)' are also used [33]. One of the most prominent predictions of a positive outcome of treatment is the presence of a communication discourse before the age of five. At the time of diagnosis, individuals with ASD are evaluated by speech therapists for the best ways to enhance a person's quality of life by resolving problems related to communication skills. If the individuals with ASD are nonverbal or have significant speech problems, the speech therapist may introduce alternatives to speech.

Pharmacological therapy

Risperidone

It was the first drug approved by the FDA in 2006 for children with autism at the age of five and above, to treat irritation associated with ASD and is a second-generation antipsychotic treatment [34]. Risperidone relieves problematic behaviors, such as mood changes, tantrums and aggressive behaviors toward oneself and others [35]. The main adverse effects of Risperidone include problems with vision, movement, symptoms of dizziness and drowsiness, as well as intestinal problems such as constipation and increase in weight [36].

Aripiprazole

This drug was approved as a treatment used to treat irritability associated with symptoms of autism for children aged 6–17 years old by the FDA in 2009 [37]. The known adverse effects include bowel problems with vomiting and constipation, as well as symptoms of dizziness, drowsiness and weight gain. Serious adverse effects may include serious problems such as neuroleptic malignant syndrome and delayed dyskinesia. The risk increases in the case of the elderly, as it is not recommended for psychosis due to dementia and may even cause death.

Materials & methods

Fuzzy PROMETHEE

Fuzzy PROMETHEE is a practical approach to decision-making toward a specific problem, its applications are classified as relatively simple compared with other approaches. Many approaches and methods have been proposed and developed to solve multicriteria problems, and fuzzy PROMETHEE is one of the MCDM methods [38]. This method is capable of imitating human reasoning ability via computers for decision-making on uncertainties. It is a set theory that is highly applicable and appropriate in creating a knowledge-based system for neurodevelopmental disorder.

The PROMETHEE technique is based on the mutual comparison of each alternative pair with regard to each selected criteria. This model is one of the efficient methods in conception and application compared with other MCDM methods. It is a user-friendly outranking method and has been successfully implemented to the real-life planning problems. PROMETHEE I and PROMETHEE II give partial and net ranking of the alternatives, respectively, while still satisfying simplicity [39]. It requires only two types of information: weights of the criteria considered and the decision-makers preference function when comparing the contribution of the alternatives in terms of each separate criteria [40]. The preference function (p_j) denotes the difference between the evaluations obtained with two alternatives (a_t and $a_{t'}$) with regard to particular criteria, within a preference degree ranging from 0 to 1. There are six different types of preference functions that can be used to implement PROMETHEE method: usual function, U-shape function, V-shape function, level function, linear function and Gaussian function. The basic steps of the PROMETHEE method [41] are as follows:

Step 1. For each criteria j , determine a specific preference function $p_j(d)$.

Step 2. Define the weights of each criteria $w_T = (w_1, w_2, \dots, w_k)$. At the discretion of the decision-maker, each weight of the criteria can be taken equally only if their importance is equal. And also, normalization can be used for the weights;

$$\sum_{i=1}^k w_k = 1$$

Step 3. For all the alternatives, $a_t, a_{t'} \in A$, define the outranking relation π

$$\pi(a_t, a_{t'}) = \sum_{k=1}^K w_k \cdot [p_k(f_k(a_t) - f_k(a_{t'}))] , A \times A \rightarrow [0, 1]$$

where p_k is the weighted average function, A is the alternative and $A \times A$ denotes the set of all possible alternative pairs. Here, $\pi(a_t, a_{t'})$ denotes the preference index that is a measure for the intensity of preference of the decision-maker for an alternative a_t in comparison with an alternative $a_{t'}$ while considering all criteria simultaneously.

Step 4. Determine the leaving and entering outranking flows as follows:

► Leaving (or positive) flow for the alternative a_t :

$$\Phi^+(a_t) = \frac{1}{n-1} \sum_{\substack{t'=1 \\ t' \neq t}}^n \pi(a_t, a_{t'})$$

► Entering (or negative) flow for the alternative a_t :

$$\Phi^-(a_t) = \frac{1}{n-1} \sum_{\substack{t'=1 \\ t' \neq t}}^n \pi(a_{t'}, a_t)$$

where n is the number of alternatives. Here, each alternative is compared with $n - 1$ number of other alternatives. The leaving flow $\Phi^+(a_t)$ expresses the strength of alternative $a_t \in A$, while the entering flow $\Phi^-(a_t)$ denotes the weakness of alternative $a_t \in A$.

Via these outranking flows, the PROMETHEE I method can provide a partial preorder of the alternatives and PROMETHEE II method can provide the complete order based on the net flow.

Step 5. Determine the partial preorder on the alternatives of A according to following principle:

In PROMETHEE I, alternative a_t is preferred to alternative $a_{t'}$ ($a_t P a_{t'}$) if it satisfies one of the following conditions:

$$(a_t P a_{t'}) \text{ if } \begin{cases} \Phi^+(a_t) > \Phi^+(a_{t'}) \text{ and } \Phi^-(a_t) < \Phi^-(a_{t'}) \\ \Phi^+(a_t) > \Phi^+(a_{t'}) \text{ and } \Phi^-(a_t) = \Phi^-(a_{t'}) \\ \Phi^+(a_t) = \Phi^+(a_{t'}) \text{ and } \Phi^-(a_t) < \Phi^-(a_{t'}) \end{cases}$$

When two alternatives a_t and $a_{t'}$ have the same leaving and entering flows, a_t is indifferent to $a_{t'}$ ($a_t I a_{t'}$)

$$(a_t I a_{t'}) \text{ if: } \Phi^+(a_t) = \Phi^+(a_{t'}) \text{ and } \Phi^-(a_t) = \Phi^-(a_{t'}).$$

a_t is incomparable to $a_{t'}$ ($a_t R a_{t'}$) if;

$$\begin{cases} \Phi^+(a_t) > \Phi^+(a_{t'}) \text{ and } \Phi^-(a_t) > \Phi^-(a_{t'}) \\ \Phi^+(a_t) < \Phi^+(a_{t'}) \text{ and } \Phi^-(a_t) < \Phi^-(a_{t'}) \end{cases}$$

Step 6. Determine the net outranking flow for each alternative

$$\Phi^{net}(a_t) = \Phi^+(a_t) - \Phi^-(a_t)$$

Via PROMETHEE II, the complete preorder can be obtained by the net flow and defined by:

$$a_t \text{ is preferred to } a_{t'} (a_t P a_{t'}) \text{ if } \Phi^{net}(a_t) > \Phi^{net}(a_{t'})$$

$$a_t \text{ is indifferent to } a_{t'} (a_t I a_{t'}) \text{ if } \Phi^{net}(a_t) = \Phi^{net}(a_{t'}).$$

Basically, the better alternative is the one having the higher $\Phi^{net}(a_t)$ value.

Fuzzy PROMETHEE applicability spans across many fields such as energy [38], nuclear medicine [42,43], material selection problems [44], cancer treatment options [44–46] and water treatment technique [47]. In this paper, we present a fuzzy PROMETHEE approach to evaluate the therapy techniques in the management of ASD and to select the best fit among all therapy technique types. The criteria are expanded and considered for the ranking, which incorporates a decision-making method dependent on multicriteria and pair correlation of available options. The augmentation of criteria is essentially created by the subject taking the issue effectively through considering the situational weight of the preferences. While addressing the ranking problem utilizing PROMETHEE, two conceivable outcomes are possible: the first gives a partial outcome and the second produces a complete ranking. To execute the technique we need two data, criteria weight and the preference function while figuring the distinction of choices commitment for individual criteria.

Table 1. Treatment alternatives and their respective parameters with corresponding values (very high, high, medium, low, very low).

Therapy techniques	ABA	CBT	Speech therapy	Risperidone	Aripiprazole
Criteria					
Cost per session	H	H	M	M	H
Duration of treatment	VH	H	H	M	M
Efficacy on social/behavioral functioning	VH	VH	H	L	L
Efficacy on irritability/aggression	M	M	L	VH	VH
Efficacy on depression	L	L	O	L	L
Efficacy on speech	M	O	H	O	O
Side effects	O	O	O	M	M
Safety	VH	VH	VH	M	M
Duration of action	L	M	M	H	H

ABA: Applied behavioral analysis; CBT: Cognitive behavioral therapy; H: High; L: Low; M: Medium; VH: Very high; VL: Very low.

Application of fuzzy PROMETHEE to therapy techniques

To evaluate therapy techniques in the management of ASD, we need to choose suitable criteria. Among the accessible criteria, we have chosen the cost of therapy per session, duration of the treatment, efficacy, side effect, safety and lastly, the duration of action of each therapy technique. As autistic children can show different symptoms, finding the best therapy can be difficult. Symptoms can range from mild to severe and can change as the child grows. Weight was assigned based on the importance of each criteria. An autistic patient may undergo one or a combination of therapies depending on the symptoms shown and the severity of the disorder. While undergoing therapy, the patient may be affected by the side effects that could present in addition to the benefits of the therapy. Therapy techniques such as Risperidone may cause moderate and manageable side effects such as movement problems, sleepiness, dizziness, trouble seeing, constipation and increased weight. However, Aripiprazole may cause dizziness, vomiting, sleepiness, weight gain, constipation and movement disorder, neuroleptic malignant syndrome and tardive dyskinesia. [Table 1](#) shows the therapy techniques, their respective parameters and corresponding values.

To successfully evaluate the therapy techniques, the triangular fuzzy scale was utilized. Weight were assigned after analyzing the important features of therapy such as the cost per session, duration of treatment, efficacy on different aspects of ASD, side effects, safety and duration of action. In this study, we conducted two experiments for two different scenarios: Child A and Child B. Child A had very severe aggression, mild depression, fairly normal speech and infinite money, while Child B with autism had no money, no aggression or depression, but severe speech and language problems. The efficacy of the therapy was assigned to the maximum weight and classified as very high for both children. This is because efficacy is the most important criteria in improving the functional abilities, quality of life and survivability of the patient. Cost per session and duration of treatment were also classified as very high for Child B due to the financial issues, while the cost was assigned to the minimum importance for Child A. Other parameters such as side effects, safety and duration of action were given lesser importance because they do not directly affect the survivability and well-being of the patients. However, families and clinicians are responsible for making the final decision on the selection of the weights based on patients' specific conditions. As a result, careful consideration should be given to each criteria before assigning weight. In this study, weight assignments were decided upon according to the several experts' opinion. It is also necessary to note that computing the outranking ratio depends on the weight assigned to the criteria. [Table 2](#) shows the linguistic variables and their corresponding fuzzy numbers, while [Table 3](#) shows the preferences for each criteria and child.

Fuzzy TOPSIS application

TOPSIS is one of the other effectively used MCDM technique constructed by Hwang and Yoon in 1981 [48]. It aims to rank the alternatives even with conflicting criteria based on the relative closeness to the positive ideal solution (PIS) by assuming that the decision-maker wants a solution, which is closest to the PIS and furthest to the negative ideal solution (NIS). In this technique, PIS contains the combination of the best points for each criteria where the NIS contains the combination of the worst points for each criteria. It can be applied only for the numerical data. Therefore, the non-numerical data need a preprocess before applying to TOPSIS technique. Even though the fuzzy

Table 2. Linguistic variables and their corresponding fuzzy numbers. Child A: severe aggression, mild depression, fairly normal speech and infinite money; Child B: no aggression or depression, no money, but severe speech and language problems.

Priority weight of criteria	Fuzzy number	Rating of criteria for Child A	Rating of criteria Child B
VH	(0.75, 1.00, 1.00)	Efficacy on depression, efficacy on aggression	Cost per session, efficacy on speech, duration of treatment
H	(0.50, 0.75, 1.00)	Safety, side effect, efficacy on social functioning	Safety, side effect
M	(0.25, 0.50, 0.75)	Duration of action	Duration of action
L	(0, 0.25, 0.50)	Duration of treatment	Efficacy on social functioning
VL	(0, 0, 0.25)	Cost per session, efficacy on speech	Efficacy on depression, efficacy on aggression

H: High; L: Low; M: Medium; VH: Very high; VL: Very low.

Table 3. Preference for the criteria for Child A and B.

Criteria	Min/max	Weight (Child A)	Weight (Child B)
Cost per session	Min	0.08	0.92
Duration of treatment	Min	0.25	0.92
Efficacy on social/behavioral functioning	Max	0.75	0.25
Efficacy on irritability/aggression	Max	0.92	0.08
Efficacy on depression	Max	0.92	0.08
Efficacy on speech	Max	0.08	0.92
Side effects	Min	0.75	0.75
Safety	Max	0.75	0.75
Duration of action	Min	0.50	0.50

sets have been presented by Zadeh in 1965, fuzzy-based MCDM techniques gained the popularity since 2000s, and these approaches have been applied in many fields after. Fuzzy sets enable to decision-maker convert the vague or linguistic data to numerical data to be used in analytical techniques [49].

The process of TOPSIS technique can be summarized as following steps:

Step 1. Construction of the decision matrix

In this step, the data of the alternatives and their features (criteria) should be determined in matrix form and the importance weights of each criteria (w_j) should be specified by the decision-maker/s where $\sum_1^n w_j = 1$. The decision-making problem with m – alternatives with n – criteria should be expressed as $m \times n$ matrix (X) in size as shown below.

$$X = [x_{ij}]_{m \times n} \quad (\text{Eq. 1})$$

Step 2. Normalization of the decision matrix

The commonly used normalization technique is given in Equation (1). And normalization of the decision matrix can be calculated by Equation (2).

$$n_{ij} = \frac{X_{ij}}{\sqrt{\sum_{i=1}^m X_{ij}^2}} \quad (\text{Eq. 2})$$

Step 3. Determination of the normalized weighted matrix

The weighted normalized matrix values (v_{ij}) can be obtained by multiplying the normalized values of alternatives with their corresponding criteria importance weights as shown in Equation (3).

$$v_{ij} = w_j n_{ij} \quad (\text{Eq. 3})$$

where $i = 1, \dots, m; j = 1, \dots, n$.

Table 4. Positive ideal solution (A⁺) and negative ideal solution (A⁻) of the autism spectrum disorder therapy techniques.

Criteria	Min/max	Child A A ⁺ /A ⁻	Child B A ⁺ /A ⁻
Cost per session	Min	0.0054/0.0081	0.0602/0.0902
Duration of treatment	Min	0.0159/0.0293	0.0566/0.1041
Efficacy on social/behavioral functioning	Max	0.0894/0.0243	0.0288/0.0078
Efficacy on irritability/aggression	Max	0.1127/0.0306	0.0095/0.0026
Efficacy on depression	Max	0.0920/0.0000	0.0077/0.0000
Efficacy on speech	Max	0.0013/0.0000	0.1481/0.0000
Side effects	Min	0.0000/0.1061	0.0000/0.1026
Safety	Max	0.0792/0.0430	0.0766/0.0416
Duration of action	Min	0.0192/0.0577	0.0186/0.0558

Step 4. Calculation of the PIS & NIS

PIS (A⁺) and the NIS (A⁻) can be obtained based on the Equations (4) and (5), respectively.

$$A^+ = (v_1^+, v_2^+, \dots, v_n^+) = \left[\left[\max_i v_{ij} \mid j \in I \right], \left[\min_i v_{ij} \mid j \in J \right] \right] \quad (\text{Eq. 4})$$

$$A^- = (v_1^-, v_2^-, \dots, v_n^-) = \left[\left[\max_i v_{ij} \mid j \in I \right], \left[\min_i v_{ij} \mid j \in J \right] \right] \quad (\text{Eq. 5})$$

where $i = 1, \dots, m$; $j = 1, \dots, n$.

i denotes the criteria aims to maximization and j denotes the criteria aims to minimization.

Step 5. Calculation of the distance to PIS & NIS

The calculation of the distances of the alternatives to the PIS (d_i^+) and NIS (d_i^-) can be determined with the help of the following Equations (6) and (7), which are defined based on the n-dimensional Euclidean metric.

$$d_i^+ = \sqrt{\sum_{j=1}^n (v_{ij} - v_j^+)^2}, \quad i = 1, 2, \dots, m, \quad (\text{Eq. 6})$$

$$d_i^- = \sqrt{\sum_{j=1}^n (v_{ij} - v_j^-)^2}, \quad i = 1, 2, \dots, m. \quad (\text{Eq. 7})$$

Step 6. Calculation of the relative closeness to PIS (R_i)

The relative distances of the alternatives to the PIS can be calculated with the help of the following Equation (8), and the highest R -value represents the most ideal alternative.

$$R_i = \frac{d_i^-}{d_i^- + d_i^+} \quad (\text{Eq. 8})$$

The ranking of the alternatives can be obtained based on their R -values. In fuzzy TOPSIS analysis, we used the same data and the importance weights as used in fuzzy PROMETHEE analysis. The distance between the weighted normalized values of the alternatives and PIS (d^+) and the distance between the weighted normalized values of the alternatives and NIS (d^-) has been calculated and shown in Table 4.

Results & discussion

The net flow shows the complete ranking results for the therapy techniques. Integration of therapy techniques has been facilitated by the embedded decision lab scenario ranking table. The resulting ranking for the therapy techniques indicates that ABA is the most preferred technique, followed by CBT, speech therapy, Aripiprazole and Risperidone for Child A, as presented in Table 5.

Table 5. Fuzzy PROMETHEE results for Child A.

Ranking	Therapy techniques	Positive outranking flow	Negative outranking flow	Net flow
1	ABA	0.0554	0.0216	0.0338
2	CBT	0.0458	0.0201	0.0257
3	Speech therapy	0.0337	0.0416	-0.0079
4	Risperidone	0.0352	0.0605	-0.0253
5	Aripiprazole	0.0346	0.0609	-0.0263

ABA: Applied behavioral analysis; CBT: Cognitive behavioral therapy; PROMETHEE: Preference ranking organization method for enrichment evaluation.

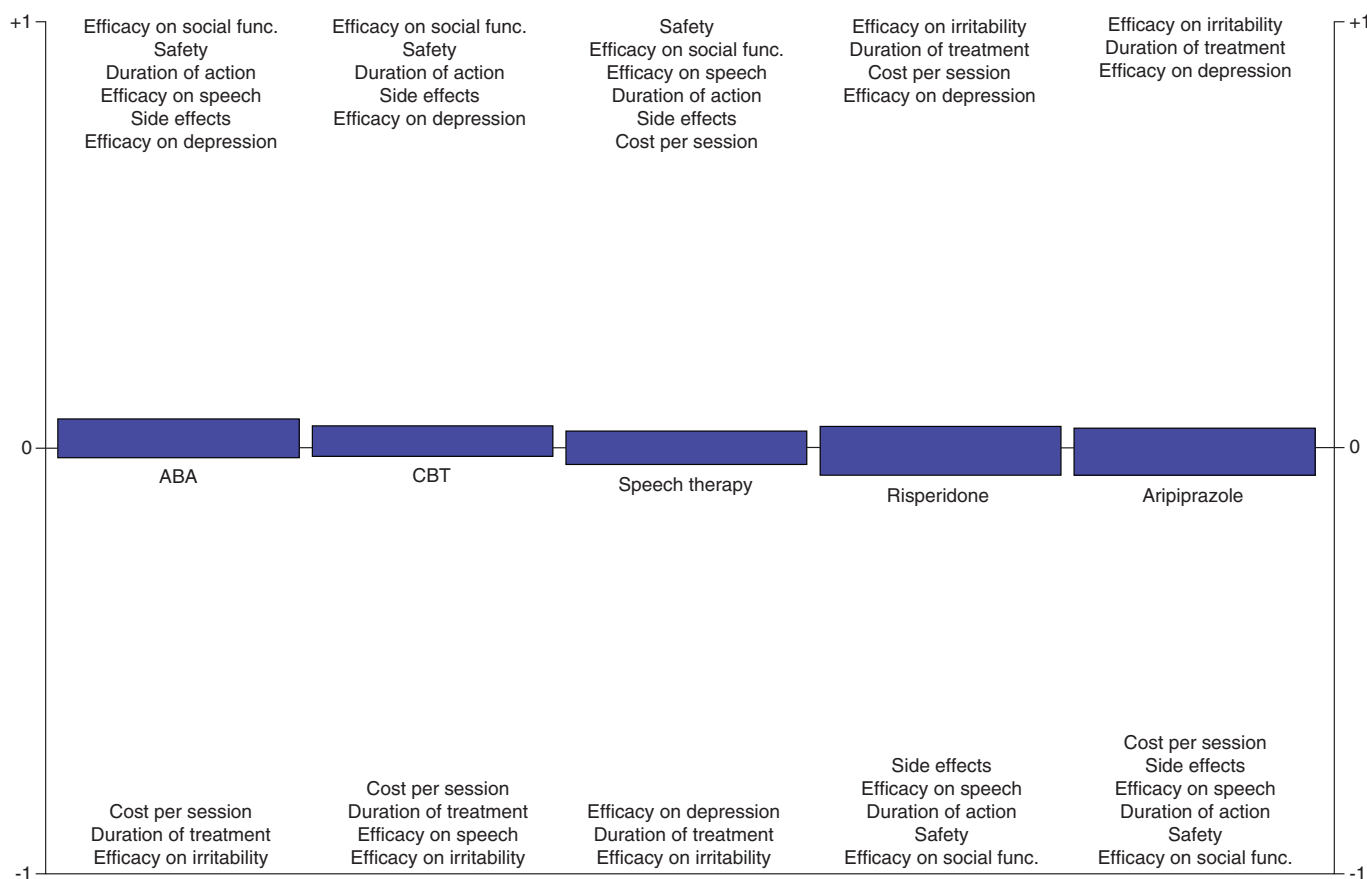


Figure 1. Positive and negative aspects of each treatment options for autism spectrum disorder for Child A. The higher the criteria stands in the graph on the positive side, the higher it contributes to the positive side of the technique. Similarly, the lower the criteria stands in the graph on the negative side, the higher it contributes to the negative side of the technique. ABA: Applied behavioral analysis; CBT: Cognitive behavioral therapy.

Figure 1 shows the positive and negative aspects of each technique based on the assigned weights. As can be observed from Figure 1, ABA has a wide positive standing for efficacy on social functioning, safety, side effects and duration of action and a narrow negative standing for cost per session, duration of treatment and efficacy on irritability. This explanation applies to the remaining therapy techniques.

The outcome for Child B is different from that of Child A. In this scenario, speech therapy came first in the ranking, followed by CBT and ABA, while Risperidone and Aripiprazole were the least preferred techniques (Table 6). Similarly, Figure 2 shows the positive and negative aspects of each therapy techniques. It should be noted that the criteria on positive and negative sides of the graph in Figures 1 and 2 for speech therapy do not change, their order in the graph changes due to the given different weights to different criteria.

With the fuzzy PROMETHEE method, clinicians are assured of making a better decision regarding the most effective therapy technique based on collective weight and preference selection either with the family of the patient

Table 6. Fuzzy PROMETHEE results for Child B.

Ranking	Therapy techniques	Positive outranking flow	Negative outranking flow	Net flow
1	Speech therapy	0.0368	0.0109	0.0258
2	CBT	0.0309	0.0144	0.0164
3	ABA	0.0399	0.0290	0.0109
4	Risperidone	0.0240	0.0445	-0.0206
5	Aripiprazole	0.0168	0.0493	-0.0326

ABA: Applied behavioral analysis; CBT: Cognitive behavioral therapy; PROMETHEE: Preference ranking organization method for enrichment evaluation.

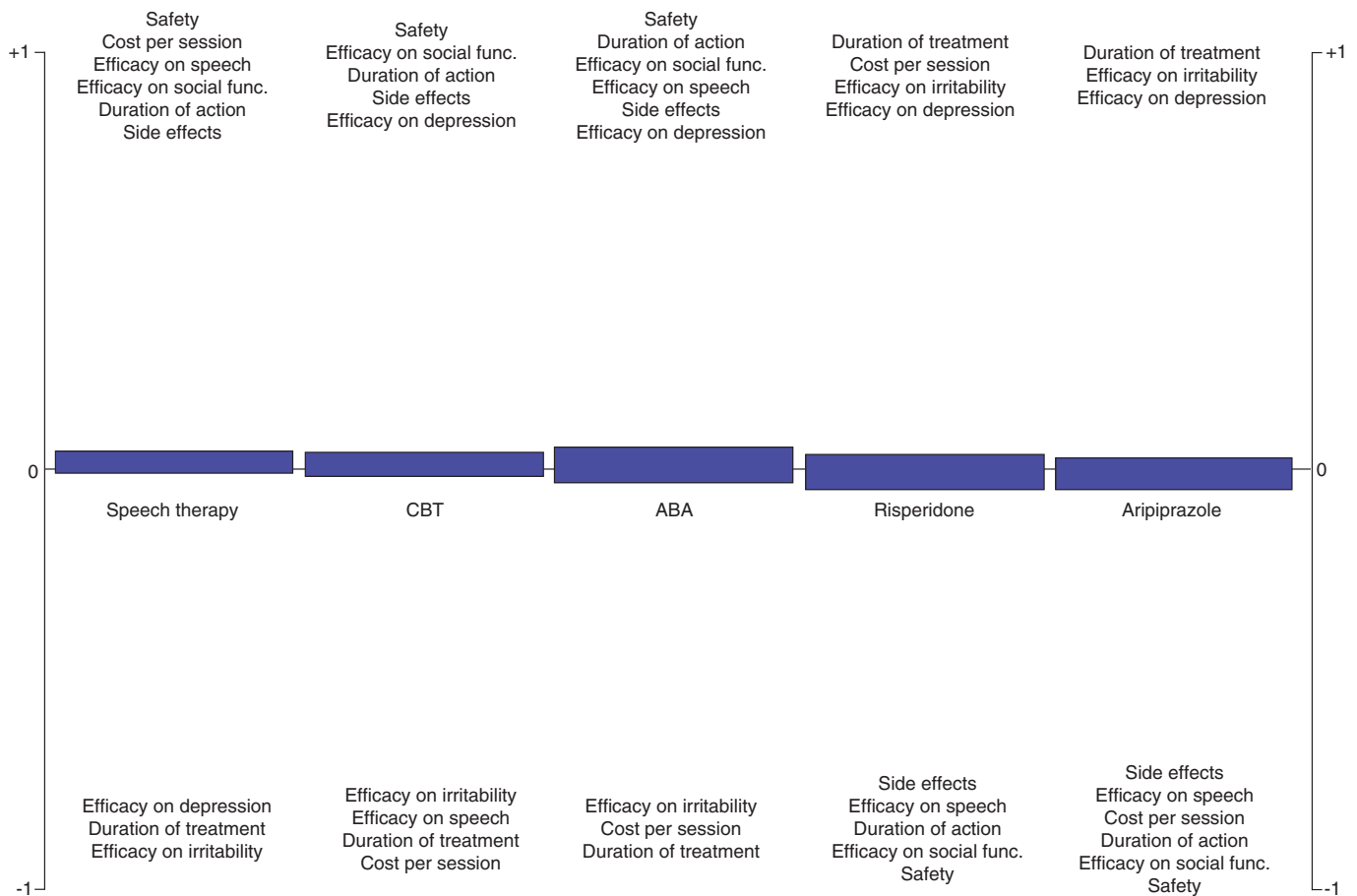


Figure 2. Positive and negative aspects of each treatment option for autism spectrum disorder for Child B.
 ABA: Applied behavioral analysis; CBT: Cognitive behavioral therapy.

Table 7. Fuzzy TOPSIS results for Child A.

Ranking	Therapy techniques	d ⁺	d ⁻	R _i
1	ABA	0.0534	0.1551	0.7439
2	CBT	0.0572	0.1502	0.7244
3	Speech therapy	0.1261	0.1948	0.6070
4	Risperidone	0.1359	0.1291	0.4873
5	Aripiprazole	0.1359	0.1290	0.4870

ABA: Applied behavioral analysis; CBT: Cognitive behavioral therapy; TOPSIS: Technique for order preference by similarity to ideal solution.

or with the health team personnel. Tables 7 and 8 below show the results obtained with fuzzy TOPSIS. As it is seen from Tables 7 and 8 for Child A and Child B, respectively, almost the same results as fuzzy PROMETHEE were

Table 8. Fuzzy TOPSIS results for Child B.

Ranking	Therapy techniques	d ⁺	d ⁻	R _i
1	Speech therapy	0.0358	0.1885	0.8403
2	ABA	0.0750	0.1529	0.6710
3	CBT	0.1549	0.1139	0.4237
4	Risperidone	0.1884	0.0572	0.2329
5	Aripiprazole	0.1908	0.0478	0.2032

ABA: Applied behavioral analysis; CBT: Cognitive behavioral therapy; TOPSIS: Technique for order preference by similarity to ideal solution.

Table 9. Preference criteria for sensitivity testing for Child A.

Criteria	Min/max	Weight (Child A)
Cost per session	Min	0.08
Duration of treatment	Min	0.25
Efficacy on social/behavioral functioning	Max	0.75
Efficacy on irritability/aggression	Max	0.92
Efficacy on depression	Max	0.92
Efficacy on speech	Max	0.08
Side effects	Min	0.08
Safety	Max	0.75
Duration of action	Min	0.50

The boldfaced value indicates the altered value for the sensitivity analysis, the side effect.

obtained with fuzzy TOPSIS. The complete ranking of the alternatives has been obtained based on the relative closeness to the PIS (R_i).

It should be noted that although the ABA tops the list of other therapy techniques for Child A, based on the need, condition and alternatives presented, preferred therapy technique for the management of ASD may differ from one decision-maker to another, as seen for the example in Child B. In addition, more than one therapeutic technique may be combined for better treatment results. The result obtained from this study does not denote a standard but shows the applicability of the method. Therefore, the result obtained by a decision-maker is not a standard as different decision-makers may come up with different solutions depending on some factors such as cost, duration of treatment, side effect, safety and duration of action. As mentioned earlier, the cost of treatment for autistic patients in the USA is expected to increase to US\$461 billion by 2025. A family having a child with ASD might not always afford the high treatment cost. Therefore, cost-effective analysis for Child B was performed by setting the weight of cost to a very high importance. A clinician/pediatrician's opinion is essential for the analysis, in terms of selecting the criteria and assigning the weight of each criteria. More research and clinical trials are needed before translating this method to the clinical settings.

Sensitivity analysis

Here, we determined how different values of an independent variable affect a particular dependent variable under a given set of assumptions. In other words, it measures how various sources of uncertainty in a mathematical model contribute to the model's overall uncertainty [50]. To apply sensitivity analysis, the weight of a criteria is altered, leaving the weights of other criteria unaltered. Hence, sensitivity analysis was done by marginally changing the values of a criteria weight from the original value as shown in Table 3 into a new value (see Table 9) and then examining that the impact that the singular decision will have on the overall result.

For this analysis, the weight of side effect was altered and changed from 0.75 to 0.08, whereas the weight for other criteria such as cost per session, duration of treatment, side effect, safety and duration of action remained unchanged. This indicates a slight change in the sensitivity of one criteria to another. The result derived from this alteration as shown in Table 10 showed that even with that degree of alteration, the results remained the same with just a slight change in the values of positive, negative and net flow ranking. CBT remained the most preferred treatment technique.

Table 10. Sensitivity test results with fuzzy PROMETHEE for Child A.

Ranking	Therapy techniques	Positive outranking flow	Negative outranking flow	Net flow
1	ABA	0.0617	0.0244	0.0373
2	CBT	0.0509	0.0227	0.0281
3	Speech therapy	0.0372	0.0470	-0.0098
4	Risperidone	0.0397	0.0670	-0.0273
5	Aripiprazole	0.0391	0.0674	-0.0283

ABA: Applied behavioral analysis; CBT: Cognitive behavioral therapy; PROMETHEE: Preference ranking organization method for enrichment evaluation.

Limitations

Assigning weights to criteria and grading alternatives are the major challenges in any study pertaining to MCDM. This is mainly due to the differences in the priorities of the decision-makers, healthcare providers, consultants etc. Sometimes, a decision-maker's priority may not be same and this will result in giving a weight they deem to be appropriate to a criteria regardless of the opinions of other decision-makers. Placing a standard would have been the solution to this disparity, but it is frequently observed that patients may exhibit different and unfamiliar responses to treatment. This warrants flexibility from the side of the decision-maker to ensure the adverse effects do not outweigh the benefits. In addressing this, sensitivity testing is always required.

In addition, individualized interventions are important in clinical setting. For example, although CBT had been demonstrated to top the list; it should be kept in mind that its applicability is very limited in intellectually disabled cases. Likewise, Aripiprazole cannot be used in a case having severe side effects of the drug like dyskinesia. In addition, improvement of domains other than irritability cannot be expected.

Conclusion

Because ASD has no cure, selecting the best therapy technique for the management of the disorder has become a necessity for therapists, parents, health institutions and researchers with an interest in neurodevelopmental disorders. This study utilized MCDM methods, fuzzy PROMETHEE and fuzzy TOPSIS. The outcome of the study indicates that ABA, CBT and speech therapy are preferred treatment alternatives, while Risperidone and Aripiprazole are to be the least effective alternatives. However, more alternatives can be included depending on the decision-maker's preference. The proposed method is unique and can consolidate both qualitative and quantitative data. It has also been demonstrated to be efficient, feasible, user-friendly and practical in decision-making for the caregiver. Other MCDM approaches could be used for comparison in future studies. Further analyses are needed to obtain more accurate patient-specific results that will incorporate specific patient demographics and data, as well as the combination of two or three techniques.

Summary points

- Autism spectrum disorder (ASD) has no known cause or cure; however, the effective management of the neurological disorder is essential for the survival of the patient.
- Based on the assigned weight to the criteria of therapy techniques and specific patient profile in this study, applied behavioral analysis, cognitive behavioral therapy and speech therapy prove to be the most preferred therapy technique for the management of ASD.
- Mathematical computation and at large multicriteria decision-making algorithm plays a crucial role in therapeutic neuroscience.
- Based on the need, condition and alternatives presented, preferred therapy technique for the management of ASD may differ from one decision-maker to another.
- More than one therapeutic technique may be combined for better treatment results.
- Pharmacological therapy does not only pose an adverse effect but also cost more when compared with the other therapeutic techniques.
- The method applied in this study can accommodate and use both quantitative and qualitative data. This makes possible a holistic evaluation of the therapy techniques.
- The result obtained from the study does not denote a standard but shows the applicability of the method.
- A clinician/pediatrician's opinion is essential for the analysis, in terms of defining and assigning the weight of each criteria.
- More research and clinical trials are needed before translating this method to the clinical setting.

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