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Section A-Research paper

ASSESSMENT OF COMBINATIONAL THERAPIES AND BEHAVIORAL INTERVENTIONS FOR ALCOHOL WITHDRAWAL SYNDROME – AN OPEN OBSERVATIONAL STUDY

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Abstract

Background: Alcohol Withdrawal Syndrome (AWS) is a common, treatable, and preventable condition characterized by nausea, vomiting, hallucinations, agitation, headaches, and disorientation to place and time. Untreated, it can lead to chronic symptoms like delirium tremens. Lack of understanding of AWS complications, lack of awareness of alcohol abstinence, and HrQOL are the most threats to disease progression. In AWS patients, Pharmacist-led education on alcohol abstinence and medication adherence are critical measures of HrQOL improvement. ***Methods:*** The prospective observational study was conducted in the General medicine department. A total of 53 patients were recruited in the study. Before and following a three-month intervention, baseline demographics, revised Clinical Institute of Withdrawal Assessment scores, and health-related quality of life scores were documented to evaluate the quality of life. The obtained results were recorded and statistically evaluated using SPSS software version 26 for Windows. ***Results and Discussion:*** Out of 53 study participants. The majority of the patients were males 98.11% and 1.8% were females. Most of them were in the age group of 39-48. All the patients were treated with benzodiazepines, anticonvulsants, and other nutritional supplements were given. There is a positive correlation between the increasing age and years of alcohol consumption ($p=0.97$, significance $= 0.492$). The health progression of participants after treatment intervention and cognitive behavioral therapy of three months led to reduced CIWA and improved HrQOL scores ($p < 0.05$). ***Conclusion:*** Our study determined that continuous education and combined pharmacotherapies have reduced alcohol withdrawal symptoms and improved patient quality of life after the intervention assessment. The implementation of both pharmacological and cognitive behavioral therapies can improve the patient's condition and enhance their quality of life.

Keywords: Alcohol withdrawal, Quality of life, Complications of Withdrawal, Cognitive behavioral therapy, Combinational treatment

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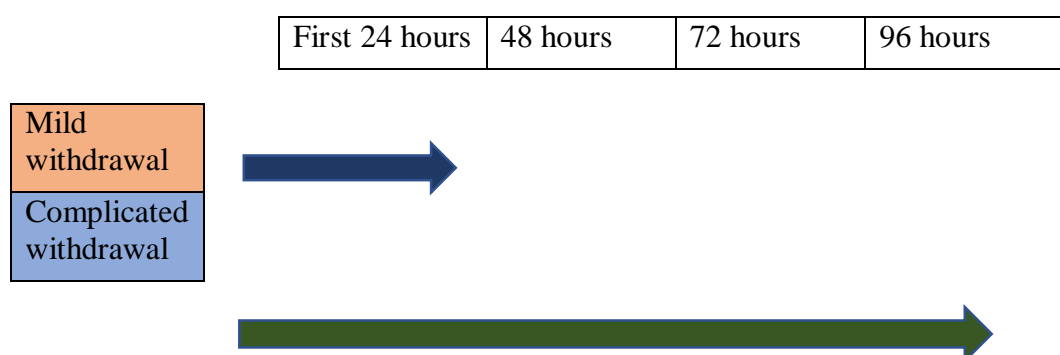
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Introduction

Alcohol withdrawal syndrome accounts for a major health problem across the world. Alcohol withdrawal symptoms occur after abrupt cessation of alcohol.[1] Individuals who abstain from alcohol consumption for a certain duration may encounter a group of symptoms referred to as alcohol withdrawal syndrome. Alcohol dependence is a highly prevalent form of psychotic illness, with a prevalence rate second only to that of major depressive disorder.[2] About 50% of people who are dependent on alcohol have withdrawal symptoms, and up to 10% have delirium tremens. [3] Withdrawal symptoms typically begin about 6 hours after the cessation of alcohol, and withdrawal seizures are frequently the first sign, occurring within 6-48 hours of the cessation of alcohol. [4]

As per the guidelines established by the American Academy of Family Physicians (AAFP), the manifestations of alcohol withdrawal encompass, [5]

1) Within 6-12 hours of cessation, individuals may experience minor hand tremors, sleep disturbances, low-level stress and anxiety, stomach upset, loss of appetite, sweating, and headaches.
2) After 12-48 hours, more severe symptoms such as hallucinations, withdrawal seizures, and general tonic-clonic seizures may occur.
3) Following the cessation of alcohol consumption, individuals may experience a range of symptoms within a timeframe of 48-72 hours. These symptoms may include delirium tremens, disorientation, sweating, as well as an increase in heart rate, blood pressure, and temperature. These central adrenergic storms cause hyperventilation, tachycardia, hypertension, tremor, heat, and diaphoresis during alcohol withdrawal. Hyperactivity causes low-grade fever. Wernicke encephalopathy causes hypothermia.

First 24 hours	48 hours	72 hours	96 hours

The above-mentioned Figure.1 depicts the severity of alcohol withdrawal symptoms with time.

The Global Status Report on Alcohol found that disorders related to alcohol consumption accounted for 1.4% of the global illness burden. Drinking alcohol is responsible for 3.2% of all fatalities (1.8 million) and 4.0% of all disability-adjusted life years lost in the United States (58.3 million).[6] The major complications of AWS include Hypomagnesemia, hypokalemia, hypernatremia, thiamine, phytonadione, cyanocobalamin, and folic acid deficiencies. Cardiac problems include Takotsubo cardiomyopathy. Pancreatitis, esophageal varices, gastritis, and hepatic cirrhosis are gastrointestinal problems. Infections include pneumonia, meningitis, and cellulitis. Neurological problems include Wernicke-Korsakoff syndrome, cerebral atrophy, cerebellar degeneration, subdural or epidural hemorrhage, and peripheral neuropathy. Delirium tremens (DT) cause rapid attention and cognitive changes, alcohol withdrawal, and autonomic instability[7-9]. To prevent the major complications of AWS, continuous pharmacist education regarding alcohol

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abstinence and monitoring the patient's medication adherence are the key indicators for improvising the HrQOL in patients with AWS. Very few studies have been conducted in hospital settings on the factors determining patients' quality of life while receiving alcoholism treatment[10,11]. So, we aimed to assess the efficacy of combinational therapies for alcohol withdrawal syndrome and behavioral intervention assessments in patients at a government tertiary care hospital in Chennai.

Aim and objectives: To assess the efficacy of combinational therapies and behavioral interventions for alcohol withdrawal syndrome.

The objectives of this study are to identify the effectiveness of both benzodiazepine, anticonvulsant use, and symptomatic care aids in the treatment of AWS. Another objective is to evaluate the effectiveness of pharmacist-led counseling for patients with AWS with an intervention gap of 3 months.

Methods

The prospective observational study was conducted for a period of 6 months i.e., from September 2022 to March 2023 in the in-patient settings of a tertiary care hospital in Chennai. Basic demographic details along with the social history of alcoholism, and days of alcohol withdrawal were interviewed with the patients.

Inclusion criteria

- Patients aged $\geq$ 18 years with alcohol withdrawal syndrome or patients with conditions such as alcohol dependence, and alcohol withdrawal seizure will be included.

- Patients who're willing to participate in this study will be

included.

Exclusion Criteria

- Patients with other co-morbid conditions that are unrelated to alcoholic liver disease complications, Patients whose CIWA score is less than 10 will be excluded.

- Patients who're not willing to participate in this study will be excluded.

Study tools

- E- Patient performa: Self-structured patient performa was designed to collect patient data such as demographic details, Drug charts, past medical history, history of present illness, and social history to interpret them.

- Clinical Institute Withdrawal Assessment (CIWA – Ar): It is the standard scale to assess the severity of alcohol withdrawal in patients, which is a 10-scale questionnaire that analyses the patient's severity of withdrawal symptoms in patients. A score less than 10 doesn't require withdrawal medications and a score more than 67 with be considered as chronic alcohol withdrawal with severe withdrawal complications.

- Validated Health-Related Quality of Life (HRQOL) Questionnaire: It's a self-structured and validated questionnaire that was used to assess the QOL of patients

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before and after treatment intervention for a period of three months. Patients were assessed based on the scoring system, and monthly follow-up was done for regular hospital visits.

Study procedure

Baseline demographic details were collected from all the patients, the assessments were done at the end of the 3rd-month follow-up among AWS patients.

Ethical consideration:

The study was initiated after obtaining proper ethical approval from the Institutional ethical committee. Informed consent was obtained from all the study participants, and also ensured confidentiality.

Statistical Analysis

Data were analyzed using SPSS software version 26. For windows. Paired t-test was used to analyze the data before and after the intervention. Pearson correlation was used to estimate the relation between the years of alcohol consumption with increasing age. A P-value of <0.05 was considered statistically significant.

Results:

The study included a total of 53 patients who met the specified inclusion and exclusion criteria. The data presented indicates that the proportion of males is higher than that of females. Among 53 patients enrolled in this study, 52 (98.11%) were males and 1(1.8%) were female. The majority of the patients 27(50.94%) found under the age group of 39-48 years, followed by 12(22.64%) patients under 49-58 years, 6(11.3%) patients under 59-68years, 6(11.3%) patients under 29-38 years, 1(1.8%) patient under 69-78 years, 1(1.8%) patient under 18-28 years. Nearly 22(41.50%) participants showed more than 20 years of alcohol consumption and 18(33.96%) participants showed 10-20 years of alcohol consumption and a minimum of 13(23.52%) participants showed less than 10 years of alcohol consumption.

The study population consisted of 53 patients, among whom a significant proportion of individuals (11.32% and 13.2%) with comorbidities such as diabetes mellitus and hypertension were found to have a high incidence of alcohol withdrawal syndrome. The occurrence of ADS and alcohol-related complications is moderately linked, while other comorbidities are associated with a lower incidence. The mostly prescribed treatment for the AWS was benzodiazepines and anticonvulsants. Among them, 53 (100%) patients received benzodiazepines-diazepam for the treatment of AWS, and anticonvulsants-gabapentin were prescribed along with 38 (71.69%) received nutritional supplements Also 8 (15%) received antidepressants and 7 (13.2%) received intravenous thiamine. The demographic details of the participants are listed in the table.1

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Table 1: Socio-demographic details of the participants

S. No	Characteristics	Variables	Frequency (n)	Percentage (%)
1.	Age	18 – 28	1	1.8%
		29 – 38	6	11.3%
		39 – 48	27	50.94%
		49 – 58	12	22.64%
		59 – 68	6	11.3%
		69 – 78	1	1.8%
2.	Gender	Male	52	98.11%
		Female	01	1.8%
3.	Years of Alcohol Consumption	< 10 years	13	23.52%
		10 – 20 years	18	33.96%
		> 20 years	22	41.50%
4.	Comorbidities	Alcohol dependence syndrome	5	9.4%
		Alcohol-related complications	5	9.4%
		DM	6	11.32%
		HTN	7	13.2%
		Others	4	7.54%
5.	Treatment	Benzodiazepines	53	100%
		Anticonvulsants	53	100%
		Nutritional supplements	38	71.69%
		Antidepressants	8	15%
		Intravenous thiamine	7	13.2%

Table 2: Relation between age and year of alcohol consumption

S.No	Mean age	Years of alcohol consumption	Total number of patients (n)	Percentage (%)	P- Value	Significance
1.	18 – 38	< 10 years	02	3.77%		
		10 – 20 years	02	3.77%		
		>20 years	03	5.66%		

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S. No		Age range	Years	No.	Percentage	P-value	Significance
2.	39 – 58	< 10 years	06	11.32%		
		10 – 20 years	11	20.75%		
		>20 years	22	41.50%	0.97	0.492
3.	59 – 78	< 10 years	0	0		
		10 – 20 years	04	7.54%		
		>20 years	03	5.66%		

P-value was determined using Pearson correlation

In a total of 53 patients, the data were analyzed by using Pearson correlation to identify the relationship between the two variables i.e. age and years of alcohol consumption. The majority of the alcohol consumers were found to be seen in the age group of 39-58 years for a period of more than 20 years and the least number of alcohol consumers were found to be seen in the age group 18-38 years for a period of less than 10 years. Table 2 depicts that there's a positive correlation between increasing age and years of alcohol consumption in increasing trend. Therefore, the P value was observed to be 0.97 and the significance was 0.492.

Table 3: Comparison of CIWA score among the participants before and after discharge

S. No	Variable	Before intervention t-score	After intervention t-score	P value
1.	Nausea And Vomiting	34.774	32.109	<.001
2.	Tremor	33.402	30.112	<.001
3.	Paroxysmal Sweats	35.322	31.196	<.001
4.	Anxiety	33.647	30.975	<.001
5.	Agitation	33.313	30.176	<.001
6.	Tactile Disturbances	36.525	33.645	<.001
7.	Auditory Disturbances	37.206	35.487	<.001
8.	Visual Disturbances	36.974	35.541	<.001
9.	Headache, Fullness in Head	34.444	31.741	<.001
10.	Orientation And Clouding Of Sensorium	37.205	33.102	<.001

P value was derived using Paired t- Test

Within a total of 53 patients, the data were analyzed by using the paired t-Test to identify the comparison of CIWA scores that is before and after intervention for a period of 3 months.

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Based on the severity of AWS the CIWA score before intervention was high and after the intervention and cognitive behavioral therapy were given the CIWA score was found to be low. Statistically significant differences were observed within the population before and after intervention with a p-value of <0.05.
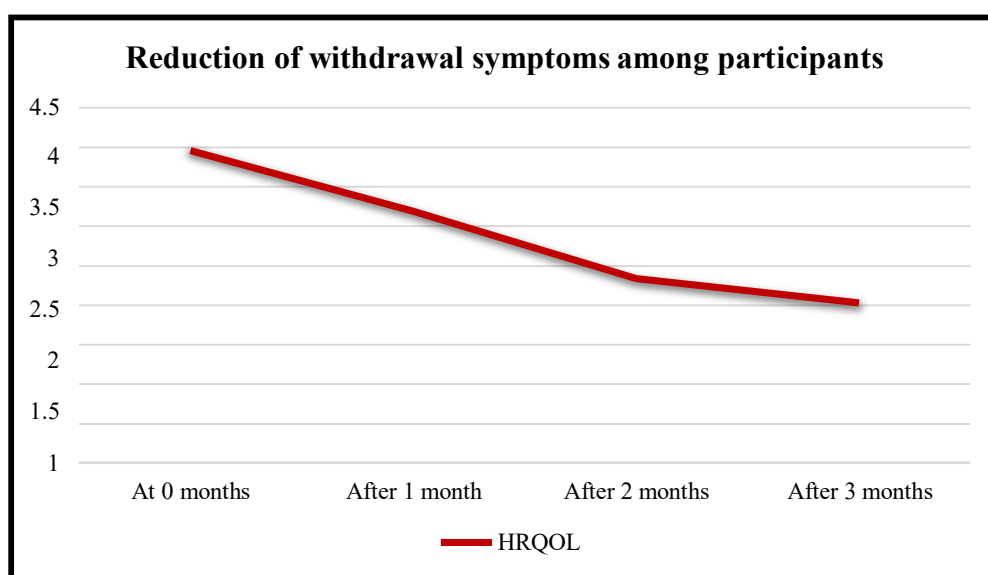
Table 4: Comparison of HRQOL among the participants before and after the intervention

S. No	Variable	Before intervention t-score	After intervention t-score	P value
1.	Have you been consuming alcohol on a regular basis lately?	31.983	37.052	<.001
2.	Do you observe progression in your health in recent days?	34.251	35.767	<.001
3.	Has your regular activities such as your profession or personal life has been affected inrecent days?	32.515	36.087	<.001
4.	Has your appetite recently been affected?	32.618	36.884	<.001
5.	Do you feel worried, anxious, tensed, or depressed now?	32.719	36.795	<.001
6.	Do you observe yourself being aggressive/ extremely angry in recent times?	32.465	36.992	<.001
7.	Does your sleep pattern seem affected?	32.580	37.000	<.001
8.	Does your relationship with your family members been disturbed recently?	32.577	36.105	<.001
9.	Do you experience withdrawal symptoms such as hallucinations, / tremors, visual disturbances/, Nausea /, and Auditory disturbances recently?	32.771	33.726	<.001
10.	Have you noticed an improvement in your psychological health in recent days?	33.753	35.742	<.001
P value was derived using Paired t- Test				

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In a total of 53 patients, the data were analyzed by using the paired t-Test to identify the comparison of HrQOL score that is before and after intervention for a period of every 15 days up to 3 months. Since the patient's alcohol consuming pattern was high and also the patient's regular activities were disturbed such as the appetite along with the patient's sleeping pattern and psychological behavior, the HrQOL score before intervention was low and after the treatment and cognitive behavioral therapy was given the patient's consumption of alcohol was reduced and also the patient's regular activities such as the appetite as well as sleeping pattern and psychological behavior were improved. It was observed that there were significant differences in the population before and after intervention with a p-value of <0.05.

Fig: Distribution of reduction of withdrawal symptoms after three months among participants

The above-mentioned figure explains the reduction of alcohol withdrawal symptoms among the participants at the end of three months.

Discussion:

A total of 53 participants participated in this study according to our estimated sample size, in which 52 participants were males and 1 was a female participant. The study involved two phases i.e., before and after intervention phases. The distribution of age among the participants shows a maximum of 72 and a minimum of 26 age was observed where the elder participants show significantly higher than younger participants; which was similar to the study conducted by _Tilman Wetterling et al_ where elder patients prevalence was higher [12] In our study among the 53 participants, male participants were 52 which was 98.11% and the female participant was 1 which is (1.8%) which indicates a higher prevalence in men than in women. Our study is similar to the study conducted by _Francisco J et al_ where the men showed higher prevalence[13] Nearly 41.50% of participants showed more than 20 years of alcohol consumption and a minimum of 23.52% of participants showed less than 10 years of alcohol consumption.

A study conducted among a huge population of about 656 patients in Poland by _Michał K Ring et al_ interpreted that the most frequent comorbid disease diagnosed among alcohol dependence syndrome(ADS) patients were essential hypertension which was found in 16.0% of AWS; diabetes affects approximately 8.1%

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[14]. Similarly in our study among 53 patients distribution of comorbidities showed diabetes in 11.32% of participants, hypertension in 13.2% and others include 7.54%.

The use of combination pharmacotherapies showed increased effectiveness in treating AWS patients, adding that it showed significant improvement in the after-intervention phase with an appropriate cognitive behavior therapy given periodically, and it is similar to the other studies performed by *Jan van Amsterdam et al* stated that the use of combinations of behavioral and pharmacological approaches in the treatment of alcohol dependence may theoretically have significant advantages and clinical treatment success may also depend on the length of the follow-up which was similar to our study results observing a significant increase in treatment success.

Multiple studies have shown that supported the efficacy of gabapentin in alcohol withdrawal treatment similarly it is efficacious in preventing relapse to heavy drinking and perhaps more importantly in promoting abstinence; which was clinically observed in our study and demonstrated that gabapentin was effective in 100% of the participants. Our study was comparable to the trial conducted by *Raymond F. Anto et al*

A study conducted by *Steven J. Weintraub* interpreted that the use of diazepam results in more rapid and safer control of symptoms and a smoother withdrawal than is achievable with any of the other benzodiazepines commonly used to treat alcohol withdrawal syndrome. The most promising agent in the treatment of AWS is the use of Benzodiazepines as the first-line treatment for patients with acute alcohol withdrawal symptoms, predominantly the results of our study under benzodiazepine use with diazepam showed 100% control of symptoms of acute withdrawal in patients with AWS.[15]

Thiamine replacement and supplements to treat nutritional deficiencies are one of the prime goals of managing AWS, it also aids in the prevention of long-term nutritional deficiencies in patients. It is important is correct abnormal thiamine and CBC levels to prevent chronic complications such as Wernicke's encephalopathy. Our study was similar to the study conducted by *Prabhat Kumar Chand et al* the supplementation of thiamine, other B-complex vitamins, and folate are important in patients with AWS due to the frequent co-occurrence of nutritional deficiencies and to prevent Wernicke's encephalopathy; the overall participants received nutritional supplementation 71.69% and IV thiamine 13.2% [16]

Similarly, our study demonstrated the efficacy of implementing structural improvements and educational interventions, which enhanced the utilization of medication-assisted treatment (MAT) for alcohol withdrawal patients, combining both pharmacological and non-pharmacological treatment modalities has significantly shown an increase in the quality of life in patients admitted with ASW, these results were similar to the study performed by *Luther Arms et al.*[17]

The relation between age and years of alcohol consumption shows maximum consumption of more than 20 years of age between (38-59 years) and minimum consumption of fewer than 10 years from (18-38 years); which shows an overall significance of 0.492. this becomes the novelty of our study where the results revealed that there is a positive correlation between age and years of alcohol consumption among the patients, where the results showed that there is a significant increase in the years of consumption with age, so it is important to evaluate the patients with acute alcohol withdrawal to prevent the further complications over the years.

The comparison of the CIWA score among the participants before and after discharge

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interprets that the participant's score shows a decrease in the severity of alcohol withdrawal symptoms after combined pharmacotherapy treatments and behavioral interventions after 3 months of continuous follow-up. All the scores recorded before and after intervention showed a significance of p-value less than 0.05, which depicts that there is a significant improvement in the severity of the participants in terms of alcohol withdrawal. In a similar study conducted by *Michelle Kane, et al* were the alcohol withdrawal team instituted a care management guideline used by all disciplines, which included tools for screening, assessment, and symptom management and concluded that results have shown a decreased number of patients who progressed to (delirium tremens) DT, AWS symptoms and other alcoholic related disorders.[18]

A study was conducted among 56 patients for 3 months to examine the prospective changes in Quality of life by *Shruti Srivastava et al* interpreted that the study confirms the poor quality of life in patients of alcohol dependence before intervention.[19] Regular follow-up with the family members in the outpatient setting enables the patients to achieve complete abstinence, thereby improving their quality of life. Our study analyzed the health-related quality of life (HRQOL) of participants pre-and post-intervention. The results indicated that the participants initially exhibited suboptimal intervention, but after follow-up, their intervention significantly improved (considering a p-value of < 0.05 as significant).

The outcomes of our study indicate that before the intervention, the quality of life of the patients was poor and no significant health progress was observed. However, following the intervention, there was a notable improvement in the patient's quality of life. A similar study with the same objective showed that measuring and monitoring the quality of life (QOL) during assessment and treatment can add important value to patient recovery, for QoL improves with treatment and successful abstinence which was done by *Chio Ugochukwu* et al.[20]

The significant reduction of withdrawal symptoms after three months among participants interprets better health progression with the help of combined pharmacotherapy and behavioral intervention as well as the assessment tools that included the CIWA-Ar scale and HRQOL have improved the quality of life and betterment in their health status. Our study adds more value and supports the use of combinational therapies i.e., the use of both benzodiazepines (diazepam) and anticonvulsants (gabapentin) will improvise the patient's condition and also aids in reducing the severity of alcohol withdrawal symptoms.[21] Adding to that, continuous education to patients regarding complete alcohol abstinence and the assessment of HrQOL are necessary to improve patient's quality of life in the long term and also help in the reduction of long-term complications of alcohol withdrawal. Furthermore, studies are required in larger populations to assess the quality of life in patients.

Conclusion: The quality of life in patients with AWS remains challenging upon pharmacotherapy alone. Medication-assisted treatments and motivational therapies are required additionally to prevent the relapse of the disease and to prevent complications. The findings of our study indicate that the implementation of ongoing education in conjunction with combined pharmacotherapies has demonstrated a decrease in symptoms associated with alcohol withdrawal, as well as an enhancement in the overall quality of life of patients upon completion of the intervention assessment. The implementation of both pharmacological and cognitive behavioral therapies can facilitate the prompt improvement of

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patient's conditions and enhance their quality of life.

Conflicts of interest: None declared

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