

Assessment of drugs and its clinical effects based on molecular frame work in neurological diseases

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ABSTRACT:

Background Drugs are the chemicals made up of aromatic and aliphatic compounds. These chemical compounds of any drug play a major role in causing clinical effects. Despite their beneficial effects they may cause unintended effect.

Aim The aim of this study is to determine the correlation between the chemical molecules of the drugs and their clinical effects in order to provide an optimal therapeutic regimen.

Method A prospective observational study was conducted in the department of Neurology at Super speciality Hospital, Coimbatore, India, for duration of six months. A total of 130 neurological disease patient's data were collected.

Results In which, 42 chemical compounds were identified and categorized based on molecular frame work, 76.2% of compounds were aromatic and 23.8% were aliphatic. Aromatic compounds were used in the treatment of stroke patients whereas aliphatic compounds were used in the treatment of seizure patients. In spite of the beneficial effects, 32.3% of patients experienced unintended effects. Aliphatic compounds (16.9%, $p = 0.037$) were causing more unintended effects than the aromatic compounds. The common unintended effect observed was hyperglycemia, caused by aliphatic homo polycyclic compounds. In patients with factors like social habits and co-morbidities ($p = 0.026$), aromatic compounds tend to cause more unintended effects.

Conclusion Knowledge of chemical compounds and its clinical effects would be essential to enable the clinical pharmacist to design a better therapeutic regimen.

KEYWORDS: Aliphatic compounds; Aromatic compounds; Intended effects; Unintended effects; Influencing factors.

INTRODUCTION

The chemical molecule of the drugs plays a major role in causing the clinical outcomes as intended and unintended effects. There are diverse reasons for an individual drug to cause unintended effects which varies from person to person [1]. By grouping the chemical compounds based on the molecular frame work and correlating with its intended and unintended effects may give a reliable and a certain outcome.

Impact of chemical molecules:

Drugs are the chemical molecules that have some kind of physiological or biochemical effects on our body. Medical management worldwide, mostly is of organic compounds and a very few is of inorganic compounds. Common features of the organic drug molecule can be better understood by organizing the structural data, which can be done by grouping the molecules of each drug into a framework, on the basis of the two-dimensional molecular structures. Molecular frame work is the union of ring system and linker atoms in a molecule [2]. The classification of drugs based on Molecular frame work as two Major classes and eight sub classes is as follows. **Figure-1**

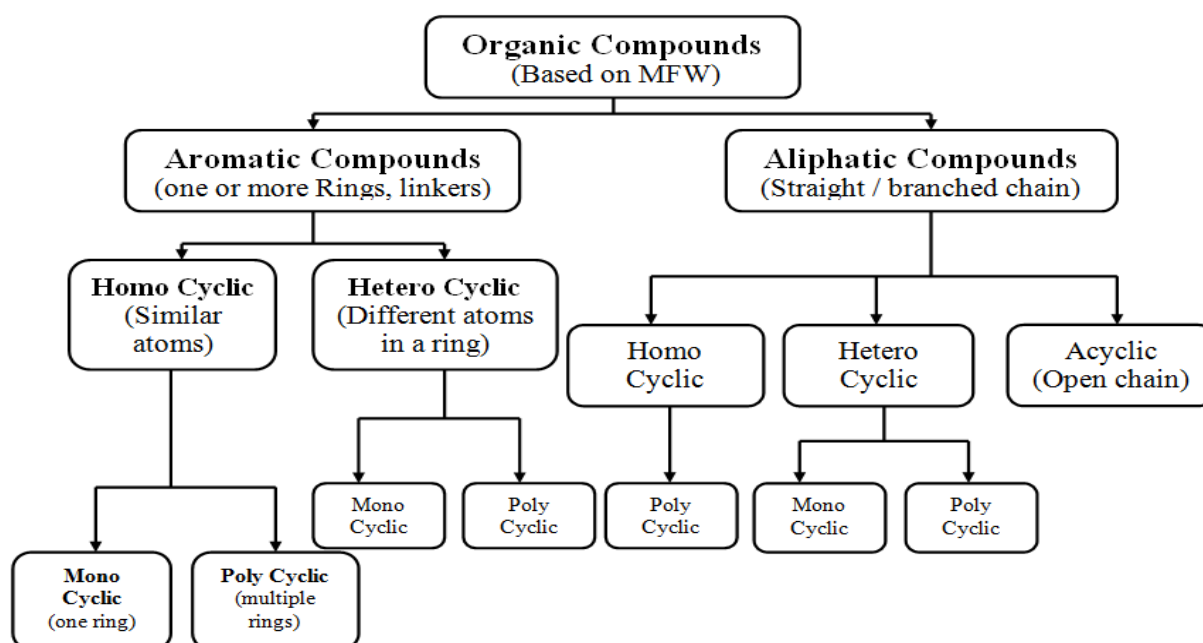


Figure 1: Organic Compounds - Classification

Exploitation of the relationship between the chemical structure and its activity is necessary to understand not only the mechanism by which a drug exerts its effect, but also how the molecular framework and physicochemical properties of the molecules influence the drugs pharmacokinetics, Pharmacodynamics property [3,4,5]. This interaction of drugs with the specific target in the body modifies their activity and results in clinical effects [6].

Further, there are some factors like social habits, co-morbidities and age which may also influence the drug in causing the unintended effects. Hence the chemical molecule of drugs and its clinical effects in patients under therapy for diseases were correlated to gain the knowledge of medicinal chemistry and the biochemical action of the drugs. Imparting this knowledge will enable the clinical pharmacists to design a better therapeutic regimen and may help in reducing the unintended effects in certain condition [7].

METHODOLOGY

Study setting and criteria:

A prospective observational study was conducted in the department of Neurology in Super Speciality Hospital, Coimbatore, India for the duration of six months from 1st March to 30th September 2020. Sample size was calculated based upon the number of inpatients and outpatients. By using Rao software sample size calculator with 5% margin of error, 95% confidence interval, 50% response distribution. Patients receiving medication for the neurological diseases were included in the study. Patients with primary diagnosis of hepatic impairment, renal failure and psychiatric illness were excluded from the study. Patient's demographic data, diagnostic details, social habits, comorbidities and medication data were collected from the medical records. Except stroke and seizure all other neurological diseases we have seen, were categorized as "other neurological diseases" (neurological diseases like Parkinsonism, Sciatica, Neuropathic pain, Generalised ballism, Intervertebral disc prolapse, Status dystonia, Lacunar infarct, palsy, Pott's spine, Vertigo, Encephalitis, Quadriplegia, Myelitis, Myasthenia gravis, Motor neuron disorder, Occipital gliosis, Guillain-Barre syndrome, Cerebral vasoconstriction syndrome and Churg-Strauss syndrome comes under the category of other neurological diseases), since the number of cases were less. Categorisation of the chemical compound was based on molecular frame work as aliphatic and aromatic compound as mentioned in Figure-1, which was used to assess the correlation between the clinical effects and the drugs.

RESULTS

A total of 130 samples were collected of which the observed male patients (n = 81, 62.3%) were more than the female patients (n= 49, 37.7%). The average age of the study population was 54 years and the majority of them belonged to the age group of above 50 years (n =79, 60.8%). Based on diagnosis, stroke (n= 71, 54.6%) was the predominant neurological disease followed by seizure (n = 22, 16.9%) and others (n = 37, 28.5%). Patients with co-morbidities (n = 77, 59.2%) and male patients with social habits (n = 45, 55.5%) were observed to be more. Hypertension (30.8%) was predominantly seen in patients with co-morbidities. Male patients with smoking (25.9%) as a social habit were predominantly seen, whereas female patients in our study had no history of social habits.

Analysis of chemical compounds

Of the 130 patients' prescription, totally 451 number of drugs were prescribed for the management of neurological diseases. Of which, 42 different types of drugs were identified. All the drugs prescribed were identified to be an organic compound and no single inorganic compounds were used. The organic compounds were classified into 2 major classes as aliphatic (19.7%) and aromatic compounds (80.3%), 8 sub classes which are demonstrated in the flow chart **Figure – 2**.

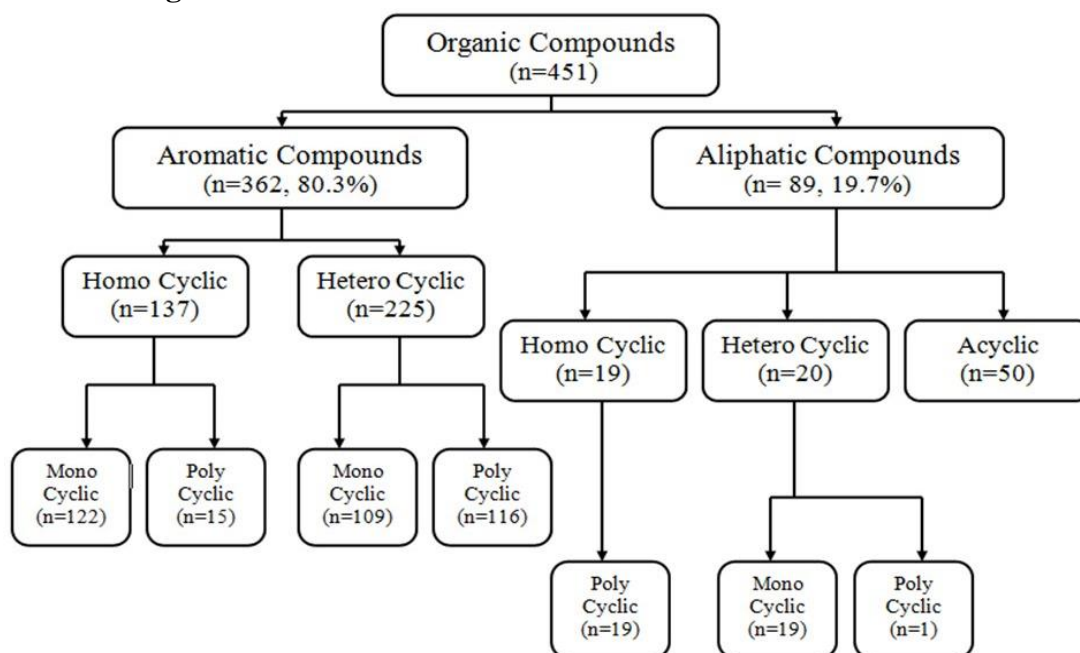


Figure 2: Categorisation of Organic Compounds

The drugs used in neurological disease that comes under aliphatic and aromatic compounds are listed in **Table 1**.

Table 1: Aliphatic and Aromatic Compounds

Organic compounds	Molecular frame work		Drugs
Aliphatic Compounds	Hetero	Monocyclic compounds	Levetiracetam
		Polycyclic compounds	Topiramate
	Homo	Polycyclic compounds	Dexamethasone
			Prednisolone
			Hydrocortisone
			Methyl prednisolone
	Acylic compounds		sodium valproate & valproic acid
			Pregabalin
			Metformin
			Mannitol

Aromatic Compounds	Hetero	Monocyclic compounds	Phenytoin
			Fosphenytoin
			precampanel
			Lamotrigine
			Atorvastatin
			Betahistine
			Amlodipine
			Torsemide
			Rivaroxaban
			Cinnarazine
	Polycyclic compounds	carbamazepine	
		oxcarbazepine	
		clopidogrel	
		Acenocoumarol	
		ticagrelor	
		chloroxazone	
		Clobazam	
		Hydrochlorthiazide	
		Rifampicin	
		Enoxaparin	
Homo	Monocyclic compounds	Piperacillin&tazobactam	
		Telmisartan	
		Benzodiazepine	
		Lacosamide	
		Aspirin	
		Paracetamol	
		Levodopa	
Carbidopa			
	Polycyclic compounds	Metoprolol	
		Tolperisone&diclofenac	
		Polycyclic compounds	Nortryptiline
			Amitriptyline

Intended effect and unintended effect

All the stroke patients receive only aromatic compounds. In seizure and other neurological disease both aliphatic and aromatic compound were used. All the neurological disease patients were found to have intended effects (n = 130), the distribution pattern of drugs was graphically represented in **Figure –3**.

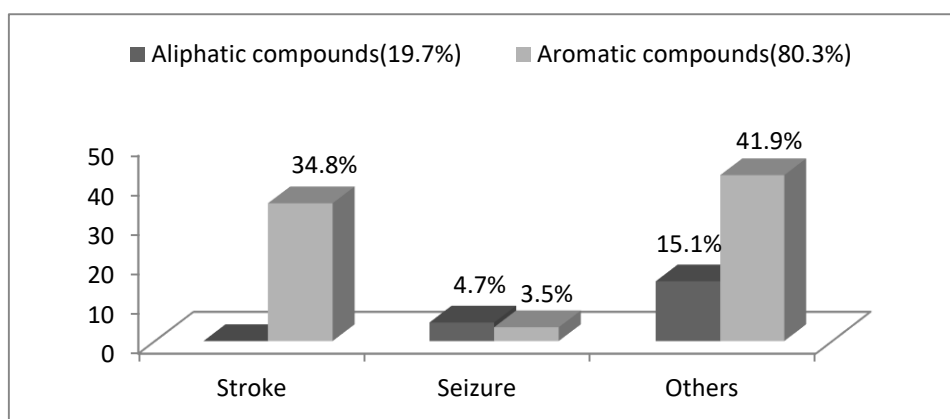


Figure 3: Percentage Distribution of major classes of chemical compounds – based on diagnosis

Despite having intended effects, the drug also causes unintended effects. Out of 130 patients, 42 were identified to have unintended effects. The unintended effects were predominantly seen in male patients (N = 25, 59.5%, $p = 0.032$) and in the patients of age above 50 years (N = 28, 66.6%, $p = 0.005$). In these 42 patients (32.3%), 26 drugs were observed to cause unintended effects. Totally 47 unintended effects were recorded. Of which 7 were aromatic compounds and 18 were aliphatic compounds. It is been identified that, aliphatic compounds caused more unintended effects than aromatic compounds ($p = 0.037$) **Table – 2**.

Table 2: Chemical compounds and its observed unintended effects

Organic compounds	Molecular frame work	No. of drugs prescribed	Cumulative no. of Compounds	No. of Patients with compounds causing unintended effects
Aliphatic compounds (n = 89)	Aliphatic hetero monocyclic	1	19	2
	Aliphatic hetero polycyclic	1	1	0
	Aliphatic Homo polycyclic	4	19	6
	Aliphatic Acyclic	4	50	7
Aromatic compounds (n = 362)	Aromatic hetero monocyclic	10	109	18
	Aromatic hetero polycyclic	13	116	9
	Aromatic homo monocyclic	7	122	4
	Aromatic homo polycyclic	2	15	1

Factors like social habit and co-morbidities have influence over the chemical compounds causing unintended effects. In male patients with social habits, aromatic compounds (44.8%, $p = 0.046$) causes more unintended effects than aliphatic compounds (4.5%) **Figure –4**. No

female patients were observed with social habit. In patients with co-morbidities, aromatic compounds (63.9%, $p = 0.026$) causes more unintended effects than the aliphatic compounds (24.6%) **Figure -5.**

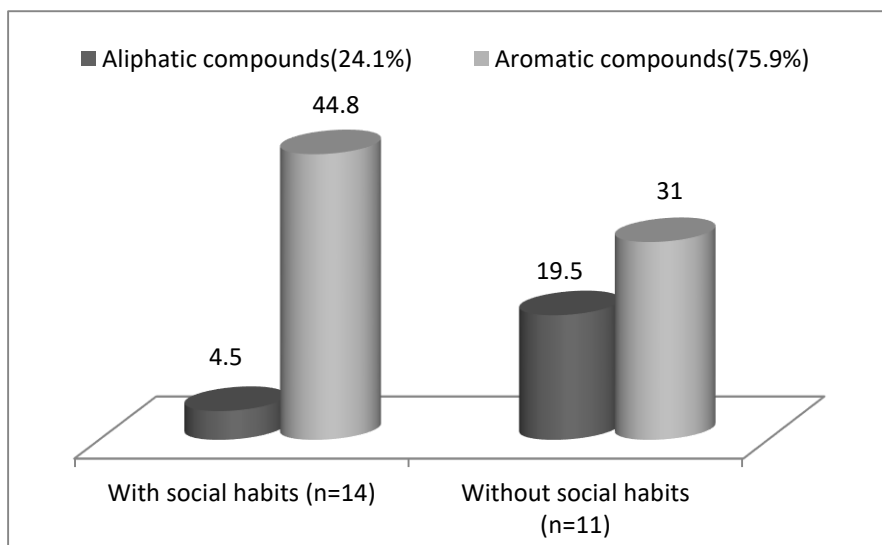


Figure 4: Chemical compounds in patients with unintended effects – Existence of social habits (n = no. of male patients with unintended effects)

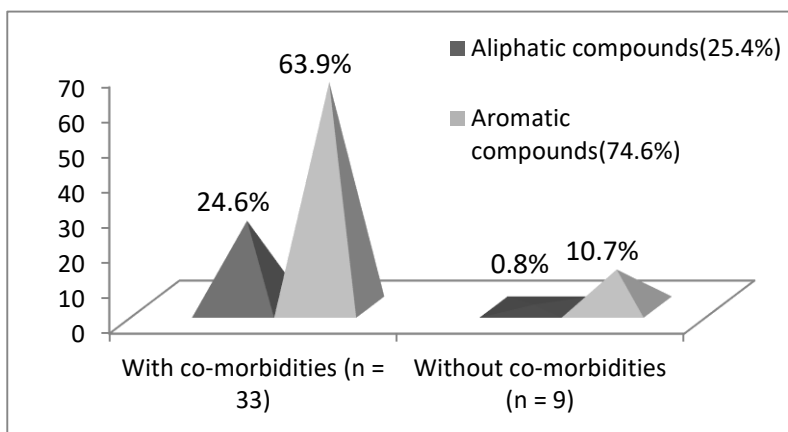


Figure 5: Chemical compounds in patients with unintended effects – Existence of co-morbidities. (n = no. of patients with unintended effects)

DISCUSSION

The data were extensively distributed based on gender, age, diagnosis, social habits & comorbidities. Out of 130 patients, 62.3% were male patients and 37.7% were female patients. The results of Janine Austin Clayton et al. (2017) were similar to our result that men are predominantly prone to Neurological diseases than women [8]. The patients of age above 50 (n=79, 60.8%) are prone to neurological diseases which was similar to the reports presented in Reliant Medical Group (2014) [9]. Stroke (n = 71, 54.6%) was the predominantly seen

neurological disease followed by seizure (n = 22, 16.9%) and others neurological diseases (n = 37, 28.5%). Smoking (25.9%) was the predominantly seen social habit. Most of the patients were observed with co-morbidities (n = 77, 59.2%, p = 0.044), hypertension(30.8%) were predominantly seen followed by diabetes mellitus (24.6%). Study conducted by Yongxing Zhou et al. (2019) reported that stroke is of higher incidence than seizure and other neurological diseases [10]. In research performed by T M Lancer, et al (1997) and sang joon an, et al (2017), most of the neurological disease patients were found to have the habit of smoking and alcohol consumption [11]. The study conducted by Iyadali, et al (2019), also shows that hypertension contribute substantially to the incidence of stroke [12]. Smoking and alcohol consumption may lead to cause hypertension which may further develop into stroke. Social habits and co-morbidities play a major role in the development of neurological diseases.

With respect to the molecular frame work of the drug, 42 chemical compounds were identified. All the drugs prescribed were identified to be an organic compound (n = 42) and no single inorganic compounds were used. The two major classes include aliphatic (19.7%) and aromatic compounds (80.3 %).The patients with neurological diseases were mostly treated with aromatic compounds (Aspirin, Atorvastatin, Enoxaparin, Amlodipine) (80.3%). Aromatic compounds(Aspirin, Enoxaparin, Clopidogrel) were effective in patients with stroke (n = 157, 34.8%, p = 0.004) and other neurological diseases (n = 189, 41.9%) (Levodopa, Amlodipine, Nortriptyline).Only aromatic compounds were used and no aliphatic compounds were used for the treatment of stroke. From the sub classes of organic compounds, aromatic hetero polycyclic compounds (Clopidogrel, Enoxaparin, Ticagrelor) (n = 60, 84.5%) were effective in stroke patients with desired anti-platelet and anti-coagulant activity.Aromatic homo monocyclic compounds (Levodopa, metoprolol, Paracetamol) (n = 72, 19.9%) were effective in patients with other neurological diseases.The study conducted by Chen Z, et al, (2000) & NF Chi, et al, (2018) describes that clopidogrel and aspirin are effective in the treatment of neurological diseases and in the prevention of recurrence which is similar to our study [13].

Cheng Xi Wei, et al, (2015) reported that most of the AED's comes under aliphatic compounds and have enhanced beneficial effects in the treatment of epilepsy [14]. Similarly Aliphatic compounds (Levetiracetam, Topiramate, Sodium valproate) were effective in seizure patients (n = 21, 4.7%, p = 0.027) in our study. In specific, aliphatic hetero monocyclic compounds (levetiracetam) (n = 12, 54.5%) have effective anti-epileptic activity which was similar to the reports presented by Bassel Abou-Khalil, it states that levetiracetam has preferred in most types of seizure due to its enhanced pharmacokinetic advantages.

All the patients prescribed with the drugs to treat neurological diseases had beneficial effects. In spite of the beneficial effects, 32.3% of patients experienced unintended effects. Unintended effects were predominantly seen in male patients (n = 25, 59.5%) and patients of age group above 50 years (n = 28, 66.6%). Study conducted by Andrew, et al (2019) reported that elderly patients were prone to increased risk of unintended effects with help of scoring methods.

Patients taking aliphatic compounds (Dexamethasone, Prednisolone, Sodium valproate, Pregabalin) ($n = 15$, 16.9%, $p = 0.037$) was observed with more unintended effects than the aromatic compounds ($n = 32$, 8.8%). In which, aliphatic homo polycyclic compounds (Dexamethasone, Prednisolone, Hydrocortisone, Methyl prednisolone) (31.6%) have greater incidence of unintended effects. Barbara, et al, (2020) reported that, hyperglycemia is a common adverse reaction of steroid (Aliphatic Homo polycyclic) therapy, affecting to 20 – 40% of patients without a history of diabetes which is associated with our result. Another study conducted by Arnon Blum, et al, (2009), which revealed that Pregabalin (Aliphatic Acyclic) may cause hyponatremia and confusion in less than 7% of population [15].

Social habits and co-morbidities are the factors that have greater influence over the patients taking aromatic compounds (Aspirin, Atorvastatin, Phenytoin, Amlodipine) in causing unintended effects. In patients with social habits, aromatic compounds (Aspirin, Atorvastatin, Phenytoin) (44.8%, $p = 0.046$) may cause more unintended effects than aliphatic compounds (4.5%). Muaed Jamal Alomar et al. (2013) reported in his study that, smoking and alcohol consumption are factors that have a crucial impact on unintended effects [16]. In patients with co-morbidities, aromatic compounds (Atorvastatin, Amlodipine) (63.9%, $p = 0.026$) may cause more unintended effects than the aliphatic compounds (24.6%). The study conducted by Jennifer R Grace, et al, (2018) shows that the prevalence of ADRs in the neurological disease with co-morbidities was high. Social habits and co-morbidities may have greater influence over the patients taking aromatic compounds in causing unintended effects [17].

CONCLUSION

Drugs are the chemical molecules or biological substances which influences the biological activity in our body. The drugs used in the treatment of neurological diseases and their associated clinical effects were analysed. All the patients prescribed with the drugs to treat neurological diseases had intended effects, despite that 32.3% of patients were identified to have unintended effects in our study. We correlated the relationship between the chemical molecules of the drug and clinical effects by classifying the drugs (chemical compounds) based on molecular framework. In terms of intended effects, we observed that only aromatic compounds (Aspirin, Enoxaparin, Clopidogrel) were used in stroke patients and they were found to be effective. Aliphatic compounds (Levetiracetam, Topiramate, Sodium valproate) were more effective in the seizure patients than the aromatic compounds. Generally, patients taking aliphatic compounds (Dexamethasone, Prednisolone, Sodium valproate, Pregabalin) were observed to have more unintended effects than the aromatic compounds (Aspirin, Phenytoin, and Amlodipine).

In patients with social habits and co-morbidities more unintended effects were observed in aromatic compounds (Aspirin, Atorvastatin, Phenytoin, and Amlodipine) than the Aliphatic compounds (Levetiracetam, pregabalin, dexamethasone). Aliphatic compounds can be suggested to patients with social habits and co-morbidities to limit the risk of unintended

effects. In patients without social habits and co-morbidities aromatic compounds can be preferred to reduce the risk of unintended effects.

Therefore, Understanding of Chemistry and the biochemical action of the drugs by imparting the knowledge of medicinal chemistry is vital in reducing unintended effects. This kind of understanding may enable the clinical pharmacist to provide a better pharmaceutical care. It also helps the health care professionals in designing the therapeutic regimen and provide a better therapeutic plan in the future.

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