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A Controlled Study of Ayurvedic Treatment in the Acutely ill Patients with Schizophrenia (Unmada) - Rationale and Results .

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Abstract

Ayurveda generally advocates multipronged therapeutic strategy comprising of both purificatory and palliative as well as internal and external drug administration for lasting relief to the patient. Thirty six patients suffering from schizophrenia (unmada) have been studied with this strategy. The efficacy of ayurvedic treatment is compared with the CPZ treated patients taking them as controls. Comparison on BPRS, ayurvedic assessment and global assessment, indicate that there is no difference between the two treated groups in their psychopathological conditions, and within each treatment group there is statistically significant reduction in psychopathology on all treatment occasions. The psychological tests confirm the efficacy of ayurvedic treatment in bringing about improvement in some of the psychological functions in the patients who received ayurvedic treatment.

Key words -

Controlled trial,
Drug treatment,
Ayurveda,
Unmada,
Schizophrenia

In this study, the efficacy of ayurvedic treatment comprising of both shodhana (purificatory) and shamana (palliative) measures was compared with that of the well known antipsychotic drug chlorpromazine in the acutely ill patients suffering from schizophrenia (unmada).

Review of Literature

Ayurvedic literature

References to unmada are available in the Vedic works. The definition, aetiology, stages and treatment of unmada including the usefulness of drugs and mantras have been described in Atharvaveda [1].

Unmada (psychosis)

Diseases have been classified in ayurveda from different view points to understand and manage them better. In one such classification diseases are categorised as manasa or manoadhisthita (psychological), shareera or shareeradhisthita (physical) and ubhayadhisthita (body-mind type). Unmada is the major type of mental disorder considered as ubhayashraya or ubhayadhisthita vikara in ayurveda [2]. It is the most descriptively dealt with manovikara and defined as the unsettled state of manas, buddhi, sanjnajnana, smriti, bhakti, sheela, chesta and achara in Charakasamhita [3]. Although a manovikara, the importance of shareerika doshas in its diagnosis and management has been clearly indicated by categorising it under shareerika doshas viz., vata, pitta and kapha [4].

Nidana (Aetiology)

Aetiological factors of unmada have been described in detail and grouped as samanya nidana and vishesha nidana. More than 30 aetiological factors have been recorded under samanya nidana of doshaja unmada. In addition to this, vishesha nidanas for each category have also been described. Likewise, 14 aetiological factors have been described under agantu unmada.

Varieties of unmada

Totally 28 varieties of unmada have been described in ayurveda [5].

Samprapti (pathogenesis)

Samanya and visesha samprapti of unmada are described in the ayurvedic classics.

Lakshana (signs and symptoms)

Seventeen samanyalakshanas (cardinal signs and symptoms) of unmada have been described, besides visheshalakshanas (specific signs and symptoms). There are more than 80 signs and symptoms attributed to doshaja unmadas - 28 in vataja, 25 in pittaja and 29 in kaphaja types. Likewise, more than 160 signs and symptoms have been recorded under various types of agantu unmada.

Poorvaroopa (prodromal)

More than 35 prodromals signs and symtoms have been recorded under dosaja unmada-purvaroopa and 14 under agantu unmadapoorvaroopa.

Manasavikara chikitsa

Ayurveda recommends three types of chikitsa viz., daivavyapashraya chikitsa (divine or spiritual therapy), yuktivyapashraya chikitsa (physical medicine), and satwavajaya chikitsa (psychotherapy), for treatingmental and physical illnesses.

Daivavyapashraya chikitsa

This refers to measures like mantra, (incantation), oushadhi (sacred herbs), mani (wearing precious gems), mangala (propitiatory rites), bali (oblations), homa (sacrifice), upahara (offerings), niyama (vows), prayaschitta (ceremonial penitence), gamana (pilgrimage) etc. (Charaka Sutrasthana 11/54). These measures are recommended in mental disorders caused by agantu (extraneous) factors and

administered judiciously after considering the nature, faith, religiosity, culture and educational level of the patient (Ch. Chi. 9/93-4). These will also be useful in certain other types of manasavikaras.

Yuktivyapashraya chikitsa

This refers totheuse of ahara (diet) and ousdhadha (drugs). (Charaka Sutrasthana 11/54).

Under ahara, it is interesting to note that different food articles like ksheera (milk), ghrta (ghee) draksha (grapes), panasa (jack fruit), brahmi (Centella asiatica) - plant, vastuka (goose foot), kakamachee (Solanum nigrum), mahakooshmanda (ash gourd), kapitha (wood apple), matulunga (Citrus medica), mahishamamsa (buffalo meat), sarpamamsa (snake meat), koormamamsa (tortoise meat), barhimamsa (peacock meat) and others, are recommended as beneficial in various mental disorders. According to an ayurvedic practitioner cuckoo meat is found to be useful in the management of certain mental disorders. These details are worthy of scientific study.

Under drug therapy, it is said that, in all types of mental diseases wher vata, pitta, and kapha are deranged, doshashodhana or srotoshuddhi (elimination of dosha or cleansing the pores) has to be done by adopting various shodhana (purificatory) measures. When the cleaning is properly done, shamanaushadha (palliatives) and rasayana (tonics) are given in order to bring back the deranged manas to normalcy.

The following are some of the oushadhas (medicines), rasayanas (tonics) and upakramas (treatment processess) that are described in the classics in treating various mental disorders.

Tonics:

1. Aswagandha
2. Kooshamanda rasayana
3. Chyavanaprasha
4. Brahmi rasayana
5. Aswagandhavaleha
6. Shatavareeleha

Medicines:

1. Brahmi ghrita
2. Kalyanaka ghrita
3. Panchagavya ghrita
4. Saraswataristha
5. Aswagandharistha
6. Saraswata choorna
7. Smritisagara rasa
8. Chaturmukha rasa
9. Manasamitra vataka
10. Unmadagajakesari rasa
11. Mahapaishacha ghrita
12. Danwantara taila
13. Unmadabhanjana rasa
14. Brahmi (Centella asiatica / Bacopa monnera)
15. Tagara (Nymphoides macrospermum)
16. Vacha (Acorus calamus)

17. Sarpagandha (Rauwalfia serpentina)
18. Jatamamsi (Nardostachys jatamamsi)
19. Bala (Sida cordifolia)

Treatment processes:

1. Virechana (purgation)
2. Basti (enema)
3. Nasya (nasal instillation)
4. Abhyanga (aneling)
5. Takradhara / Ksheeradhara / Tailadhara / Kashayadhara (Streaming of medicated buttermilk / milk / oil / decoction, on the forehead of the patient)
6. Mastishkya (application of medicated wet cakes on the vertex)
7. Shirolepa (application of medicated wet cakes on head)
8. Dhoopana (fumigation)
9. Anjana (collyrium)
10. Raktamokshana (blood letting)

Satwawajaya chikitsa

The aim of this therapy is to restrain mind from desire for unwholesome objects. (Charaka Sutrasthana 11/54). This permits considering, occupational, behavioural and like therapies as well, since the ultimate aim of them also would be to restrain mind from unwholesome objects.

Speaking on the role of the verbal interaction with the patient, it is indicated that, soothing words of consolation from a compassionate relative or friend, would help a great deal in solving the problems of the patient. This clearly indicates the qualities expected of a therapist if the therapy administered has to be beneficial to the patient. The best approach to achieve the goal of satwajayachikitsa is through jnanam (knowledge), vijnanam (analytical thinking), dhairya (courage), smriti (scriptural learning), and samadhi (concentration). (Charaka Sutrasthana 1/58, Chikitsasthana - 9/79). Mental disorders caused by kama (excessive desires), shoka (grief), bhaya (fear), krodha (anger), harsha (excitement), irsha (jealousy), moha (infatuation) should be countered by carefully inducing the opposite passion in order to neutralise the causative ones. (Charaka, Chikitsasthana. 9/86).

The above approaches can be said to be more useful in such manasavikaras that are comparable to certain neurotic conditions caused due to external psychological reasons.

Apart from these, measures like calming the patient with assurances and words of religious and moral import, shocking him by announcing the loss of something he holds dear, or showing him some wonderment, threatening him by physical restraint etc.have also been mentioned. (Charaka chikitsasthana 9/31).

II. Modern Literature

Psychosis

Patients are described as psychotic when their mental functioning is sufficiently impaired to interfere grossly with their capacity to meet the ordinary demands of life. The impairement may result from serious disturbance of their capacity to recognise reality. Hallucinations and delusions for example,

may distort their perception, attention or mood. This may be so profound that the patient's capacity to respond appropriately is grossly impaired. Deficits in perception, language and memory may be so severe that the patient's capacity for mental grasp of his situation is effectively lost. The present study includes only functional psychosis, that is not caused by organic lesion of the brain.

There are four broad categories of functonal psychosis

(1) Schizophrenia
(2) Affective psychosis
(3) Paranoid states and
(4) Reactive psychosis.

These categories have been sub-classified into different categories.

Schizophrenia

The term schizophrenia is used here for a group of mental illnesses characterised by specific psychological symptoms and leading in the majority of cases to a disorganisation of personality of the patient. The symptoms interfere with the patient's thinking, emotion, perception and motor behaviour, each in a characteristic way.

Types:

(1) Simple
(2) hebephrenic
(3) Catatonic
(4) Paranoid
(5) Schizophrenia with atypical and mixed clinical picuters.

Treatment of schizophrenia

General

Treatmentl of schizophreniaon modern lines consists of the judicious combination of physical, psychological and social methods of treatment.

Insulin coma therapy which used to be the first line of treatment in schizophrenia is now only of historical interest.

Electro-convulsive therapy is useful for relieving depressive symptoms and many of the florid manifestations of schizophrenia.

The first drug to be used in the treatment of schizophrenia in the new series of psychotropic drugs, was reserpine but there were disadvantages in that it took many weeks to produce the beneficial effects. There were phases of turbulance and some times severe depression occurred as a side effect.

The phenothiazine derivatives have now taken the place of pride in the drug treatment of schizophrenia.

For the acute and disturbed schizophrenic patient chlorpromazine is still the standard drug (Kalinowsky and Hippins 1969).

Work therapy and occupational therapy are important in promoting recovery and preventing deterioration.

Review of work done

Hakim [6], Soni [7], and Rana [8] have reported studies using 'Siledin' (combination of various indigenous drugs) in the treatment of various mental disorders and observed encouraging results.

Kale [9] also used the above compound drug in the management of 388 patients suffering from different mental disorders which also included 112 'schizophrenic-reaction-type' patients. For this particular category the control group consisted of 30 cases. The 'affective reaction type' (M.D.P) group consisted of 206 patients. The control group consisted of 70 cases. The control group was treated with various physical methods alone. The trial was for a period of two months. Each tablet being 400 mg the daily dose varied from 3-12 tablets. The indigenous medicine was given either alone or in combination with other modern drugs and/or concurrent E.C.T. Assessment was done on the basis of mental examination and the outcome was classified into cured, improved and not improved categories. The results show a cure of 59.9% in the affective group and the schizophrenic group, whereas the 'cure' in the control group, whereas the 'cure' in the control group was only 36%. In the patients treated with indigenous drugs alone, no serious side-effects were observed. However, it is difficult to comment on this study as the criteria for the selection of the patients and the methodology are not available in the reported study.

Fozedar [10] used the indigenous drug Vacha (Acorus calamus) in 28 patients of anxiety neurosis and 75 schizophrenic patients, for 3 weeks. The drug was given orally in the form of tablets. The author reports that 11 patients of anxiety neurosis showed an improvement of 50% and above, and out of these, 6 patients showed improvement over 75%. Among the schizophrenics 16 patients showed improvement of 50% and above, out of which 7 patients showed improvement over 75%. The schizophrenics were given a much higher dosage (60-90 grains) as compared to those of anxiety neurosis (10 grains).

A study using 'Soberin', a combination of indigenous drugs was used in mental patients and the author claims encouraging results [11].

An indigenous drug 'Nuvon', a combination of 11 ingredients was administered in a double blind trial on 44 hospitalised schizophrenic patients. Twentytwo patients were given the drug, and the remaining, identical placebo talets. Results revealed that there was no complete recovery with the drug. Three patients in the experimental group and one patient in the control group showed partial improvement and there was no improvement in the remaining patients [12].

Malakangani oil alongwith other indigenous drugs was administered in an uncontrolled trial on a group of mental patients which also included 6 schizophrenics and 30 depressives by Hakim [13]. On the basis of subjective assessment he claimed that 73.3% recovery was observed in the depressives whereas none of the 6 schizophrenics showed any significant improvement [13].

Cuckoo meat was found to be effective in the management of different kinds of mental diseases, studied by Chatterji [14].

The efficacy of Brahmyadiyoga a herbal compound consisting of Brahmi (Centella asiatica), Sarpagandha (Rauwolfia serpentina), Vacha (Acorus calamus), jatamamsi (Nardostachys jatamamsi), Tagara (Nymphoidis macrospermum) and Kustha (Saussurea lappa), and single drug Tagara in the management of acute schizophrenia was studied in a double blind controlled study. The efficacy of

these drugs was compared with that of chlorpromazine and placebo. Brahmyadiyoga was found to be significantly better than placebo and Tagara. The difference between Brahmyadiyoga and chlorpromazine was not statistically significant though overall improvement was better in CPZ group. The difference between Tagara and placebo was not significant [15]. In a retrospective study of 182 cases of unmada treated on Ayurvedic treatment, it was found that the general ayurvedic treatment given was effective in 88% of the cases treated [16].

Brachmyadiyoga was tried on 14 chronic schizophrenics in a pilot study. Seven out of ten patients who underwent treatment for three months and all the four two months improved [17].

Ayurvedic Research Unit CCRAS, NIMHANS, has prepared a monograph titled 'An approach to mental examination based on Ayurvedic concepts' with guidelines, facilitating its implimentation [18]. This worked is based on the definition of unmada as given by Charaka. Besides aiding clinical diagnosis in various mental disorders and their treatment, this work would also enable detection of the particular dimension or dimensions of manas affected in a given mental illness.

In a double blind controlled study, the efficacy of Brahmyadiyoga was compared with a known antipsychotic drug chlorpromazine (CPZ) and a Placebo in patients suffering from chronic schizophrenia (anavonmada). The study has revealed that Brahmyadiyoga is better than placebo. CPZ was significantly better than both Brahmyadiyoga and placebo [19].

A compound formulation containing five potent medhya drugs was tried by a team of ayurvedic experts in patients of unmada (psychosis). The treatment was found safe and effective [20].

Material and Methods

(i)**Sample:**

Thirtysix patients of either sex in the age range of 16 to 45 years suffering from schizophrenia with active psychotic symptoms of a minimum duration of one month were selected for the study. Patients with chronicity of more than 10 years and physical complications or other diseases like epilepsy, mental retardation etc. were excluded from the study.

Out of the 36 patients elected, eighteen were studied in each group (ayurvedic and CPZ group). Of them two were dropouts, since they left hospital during the course of the treatment and; three patients were rejected (two on account of revised diagnosis and one patient on account of being given a different antipsychotic drug.

(ii)**Diagnosis:**

Psychatric diagnosis was done on the basis of ICD 9 (WHO). Ayurvedic diagnosis was done on the basis of definition and symptoms of unmada as given by Charaka.

(iii)**Type of study:**

It was a rater blind study.

(iv)**Nature of control:**

Efficacy of ayurvedic treatment was compared with a known antipsychotic drug. In view of different types of ayurvedic treatments that are being chosen in treating the patients, it was not possible to have identical treatments in both the groups. Control group was administered standard modern treatment.

(v)**Assessments:**

a) Ayurvedic assessment was carried out on the basis of

(i) the examination of mental aspects i.e. manas, buddhi, sanjnajnana, smrti bhakti, sheela, chesta and achara, and

(ii) presence of the lakshana of various doshaja unmada as explained in the ayurvedic classics and as detailed in our monograph [18].

The assessments were carried out on a rating scale structured for this purpose. The scores for various items were given considering their clinical importance, based on earlier studies.

b) Psychiatric assessment was done on the basis of the Brief Psychiatric Rating Scale (BPRS).

The ayurvedic and psychiatric assessments were done initially and weekly thereafter.

c) Psychological assessment: Psychological assessment focussed on assessing cognitive functions thatare generally considered sensitive to improvement during treatments. The functions chosen are behavioural arousal and alertness, information processing, learning and memory functions and ideational fluency. Psychological assessments were doneinitially before the commencement of the treatment and finally after the completion of the treatment. The tests administered were Reaction-Time, Vigilance, Learning and memory function test - verbal form and ideational fluency.

Reaction Time [21]**:**

The test consisted of simple and choice items using standard techniques. Both the series consisted of 10 practice trials followed by 20 test trials each, and RT was recorded in milliseconds.

Vigilance [22]**,** [23]**:**

Two series of two auditory stimuli paired at random, with one occurring infrequently were presented to the subject with a change in the random order of presentation in the second series. The number of infrequent signals correctly detected constituted the score of this test.

Learning and memory functions test [24]**,** [25] **/ Verbal form :**

Two passages were used for the verbal form of the test. The test employed immediate recall over three consecutive trials and a delayed recall. The test indicated improvement by learning as well as loss of information if any during delay.

Identical fluency:

Here the subject made structured free association by naming objects made of wood, iron and round objects, on different trials. The number of average correct responses was recorded [26].

(vi)**Investigations:**

Following investigatioins were carried out before and at the end of the treatment.

(i) Blood for T.C., D.C., E.S.R., urea and liver functions

(ii) Urine for sugar and albumin

(iii) Body weight, and

(iv) E.C.G.

(vii)**Treatment:**(1)

Ayurvedic treatment (Ay. group)

In this study it was intended to examine the combined effect of the general line of ayurvedic treatment

comprising of shodhana (cleaning) and shamana (palliative) measures and satwawajayachikitsa (psychobehavioural therapy) as follows:

1. Snehapana: Kalyanakaghrita for 3-7 days increasing @ 10 ml daily, daily 15 ml.
2. Ayushman 13 (Brahmyadiyoga 500 mg) 2-2-2 (Annexure-II). Ayushman 14 (Nidrakarayoga) - 2-0-2.
3. Mridu abhyanga with Dhanwantara taila for two days after snehana followed by bhaspasweda with hot water.
4. Virechana kashayya - 75 ml (with 1- 2 Ichabhedi pills whenever required). This Kashaya was prepared by boiling 10 gms each of Aragwadha, Hareetaki and Draksha in 150- ml of water and reducing it to 75 ml). Item 2 was stopped for 2 days i.e. on the day of Virechana and the following day.

Where the symptoms did not subside by 50% by the 15th day of the start of treatment, the following treatment was given.

1. Kalyanakaghrita in case of Vatapittonmada and Panchagavya ghrita in case of Kaphonmada-10 ml once.
2. Item 2 and Unmadagajakesarirasa 200 mg plus Sootasekarasa 200 mg b.i.d.
3. Item 3 was given weekly 3 times
4. Saraswatarista 10 ml and Aswagandharista 10 ml - b.i.d. after meals.

If the patient was withdrawn and less active, Ayushman 16 (Vishadahara yoga - Annex - II) was given in place of Ayushman 13 (Brahmyadiyoga) along with other drugs for 2 weeks. For patients who were hyperactive, restless and who had sleep disturbance, mastiskya with Amalakichoorna 20 gm, Kustha 10 gm, Karpoora 500 mg and Khasakhas 20 gm was used with plain water dailiy 2-4 times.

In addition to the above, patients from both the groups were allowed to play or were sent to OCT (Occupational therapy).

2.

2. Modern treatment (CPZ group)

(1) Antipsychotic: Tab. chlorpromazine 300 mg/day was started as minimum dosage, which was further increased to 600 mg per day after 15 days if the improvement was less than 50%.

(2) Anticholinergics - Tab Trihexiphenidyl HCl 2 mg was started alongwith the antipsychotic drugs to reduce the complication of extra pyramidal symptoms.

(3) Minor tranquilizers - Inj. Diazepam or tab. Diazepam was administered in unmanageable cases in both Ayurvedic and CPZ groups.

Duration of treatment: Twenty-eight days.

(viii)**Age**

The mean age for the two treatment groups are as follows:

The difference of mean age in two treatment groups is not significant.

(ix)**Duration of illness:**

The mean duration of illness for the two treatment groups is as follows:

The difference in the distribution in the two groups according to duration of illness is not significant.

(x)**Initial score**

The mean initial score for the two treatment groups is as follows:

Results

A) Results of the psychiatric and ayurvedic assessments, between the group and within group comparisons are given in Tables I to IV and Figures 1 to 4.

Table I - BPRS total psychopathology scores through successive psychiatric assessments in the two treatment groups

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It may be noted that the psychopathology mean score was significantly higher in CPZ group initially. But the two groups did not differ in any of the subsequent occasions. This holds good even when corrected for initial difference.

Table II - Reduction in psychopathology score through successive psychiatric (BPRS) assessments (Initial compared to first, second, third and fourth assessments) within each of the two groups

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Table III - Psychopathology on Ayurvedic assessment (manas and symptoms score) through successive assessments in the two treatment groups

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Table IV - Reduction in psychopathology on Ayurvedic assessment (manas and symptoms) within each of the two treatment groups

Table IV - Reduction in psychopathology on Ayurvedic assessment (manas and symptoms) within each of the two treatment groups

- ***Mean total psychopathology score on psychiatric (BPRS) assessment***
- ***Mean total score Ayurvedic rating (Means)***
- ***Mean total score Ayurvedic rating (Symptoms)***
- ***Categorywise percentage of patients on clinical global improvement***

B) Improvement on the basis of global assessment in the two treatment groups.

t=0.2534, d.f.=29, P > 0.10

Comparison on psychiatric rating scale (BPRS), ayurvedic assessments, and global assessments indicate that
(a) there is no difference between the two treatment groups in their psychopathological conditions,
(b) within each treatment group there is a statistically significant reduction in psychopathology on all assessment occasions.

(c) Psychological Assessment

Table showing means and standard deviations of psychological tests scores within groups

The between group comparison was done by F test. The results on the reaction-time test showed no evidence of a significant difference between the two treatment groups. The two treatment groups did not differ on simple reaction time measure whereas a significant difference ($P < 0.05$) was noticed on the choice reaction time measures. Brahmyadiyoga treatment group showed higher reaction time as compared to CPZ group.

There was no significant difference between the means of various other tests in the initial assessment. A similar picture emerges in the final assessment as well. The two groups with different modalities did not show evidence of a significant difference on the various tests except the choice reaction time.

Paired t test was done to determine the difference within the groups between the initial and thefinal assessments. Significant improvement was seen on tests of vigilance, verbal learning and memory functions in both the groups. The improvement seen in the CPZ treatment group was found to be greater than that seen in the Brahmyadiyoga treatment group. However this difference was not statistically significant.

Significant improvement was seen on some of the psychological tests after the administration of Ayurvedic treatment. That the two groups did not significantly differ in the final assessment on any of the tests indicates that the Ayurvedic treatment could have been almost as effective as the CPZ treatment. However, significant improvement in the Ayurvedic group was seen on fewer tests as compared to the CPZ group. Nevertheless they are indicative of a significant improvement in the cognitive functions of the patient. That the difference in scores (between initial and final) between the two groups did not significantly differ, further confirms the efficacy of the Ayurvedic treatment in bringing about improvement in some of the psychological functions in the patients.

Investigations

There was no significant before and after effects on before and after comparison, as well as on between group comparison on various laboratory investigations and ECG.

Discussion

Since schizophrenic patients were the primary selection criterion and these patients fell into different doshic types from ayurvedic point of view, the treatment was scheduled in a general way to take care of these doshic differences.

Chlorpromazine is well established for its antischizophrenic effect. The ayurvedic treatment possessed vyadhipratyaneeka and doshapratyaneeka qualities.

Earlier studies have shown that the difference between ayurvedic treatment (Brahmyadiyoga) and chlorpromazine was not statistically significant [15] and ayurvedic general lines of treatment is effective in 88.5% oft patients of different types of unmada (Ramu et al). Hence the results of both treatments in unmada (schizophrenia) patients is only as expected. This suggests that the ayurvedic treatment is efficacious against unmada atleast to the level of that of the standard drug chlorpromazine.

Due to constraints of having to administer the ayurvedic treatment within the limitations of a rigid schedule as expected in modern research methodology, it was not possible to fully exploit the ayurvedic treatment. In the ordinary course, ayurvedic treatment is optionally given by sensitively adjusting dose, combination on the basis of dosha, dushya, bala, prakriti etc.

There is further need to take up studies to assess the relative efficacy of various compound preparations as well as the individual ingrediants with a view to refining the regimen. It is also desirable to work towards the preparation of total extract to reduce the bulk and permit to work with larger doses in needing cases. A further aspect that needs to be looked at is the probability of relapses and occurrence of any long term adverse effects. Modern drugs are already known to have certain neurotoxic effects especially the movement disorders. If the ayurvedic drugs are demonstrated to be free from such effects even on long term use that would be a matter of great theoretical interest and practical use.

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