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Title: Evaluation of Integrative Medicine Supplements for Mitigation of Chronic Insomnia and Constipation in an Inpatient Eating Disorders Setting

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Abstract: Objective: To determine whether patients with eating disorders used fewer conventional sleep and constipation medications when given integrative medicine interventions.
Method: Retrospective data from two cohorts were compared; one group received only conventional treatments for insomnia and constipation (ED), and the other received integrative medicine and conventional treatments if needed (IMED). Patient reports of insomnia and constipation as well as medication use for these conditions were collected and compared.
Results: Patient demographics were similar in the two groups. Although reports of 'slept well' were similar, use of conventional sleep medications was significantly lower for the IMED group. Reports of constipation and use of conventional constipation medications were also lower for IMED vs. ED, but these differences were not all statistically significant.
Conclusion: Integrative medicine interventions for insomnia and constipation appear to benefit patients with eating disorders and may allow these patients more focus for the work of recovery.

Evaluation of Integrative Medicine Supplements for Mitigation of Chronic Insomnia and Constipation in an Inpatient Eating Disorders Setting

Chronic insomnia and chronic constipation are common problems for patients with eating disorders.(1-4.) Although neither of these symptoms is central to these patients' pathologies, both reduce the energy and attention available to devote to the work needed for recovery and create barriers to refeeding. Conventional treatments for these symptoms are also problematic. Many sleep medications are addictive and have a number of undesirable side effects, including nausea and anorexia. Laxatives can augment the purging behaviors of many patients with eating disorders, and long-term use can create dependence and electrolyte imbalances.

Several alternatives to conventional sleep medications exist, including sleep hygiene, melatonin, L-tryptophan or 5-hydroxytryptophan, and herbal formulas that contain valerian or kava kava.(5-10.) While there are many over the counter preparations for constipation, many of them work in a very similar manner to prescription laxatives and are often abused by patients with eating disorders. Other alternatives include fiber supplements, which are generally safe, but often have side effects such as gas, bloating, and abdominal pain—all of which can create barriers to the refeeding process in this vulnerable population.

The purpose of this study is to evaluate the impact of an integrative medicine eating disorders (IMED) program in reducing the prevalence of these conditions in an inpatient population with eating disorders (anorexia, bulimia, binge eating disorder, and compulsive overeating) at a private inpatient psychiatric hospital. Our primary hypotheses are that compared with patients on the previous eating disorders program, patients on the new IMED program sleep better and use fewer conventional medications for sleep, and that they have fewer complaints of constipation and use fewer conventional medications for constipation.

METHODS

This retrospective controlled study used data obtained via chart review to compare reported insomnia and constipation rates and actual sleep and constipation medication use for a 6-month cohort of patients on the IMED program and a 6-month control cohort who completed treatment on the previous eating disorder (ED) program. Before initiation this study was reviewed and approved by both the hospital's human subjects committee and the University of Arizona's Institutional Review Board.

Subjects

The treatment (IMED) group consists of the entire cohort of IMED patients admitted to the hospital's eating disorder program during the 6-month period from June 1 through November 30, 2005. This period represents the first 6 months during which the IMED program was considered to be completely "up and running." This cohort's data were

compared with a control (ED) cohort consisting of all patients admitted to the hospital's eating disorders program in the 6 months just prior to the beginning of IMED program development (i.e., the 6 months prior to December 1, 2004).

Interventions

The IMED program brought a number of changes to the ED program previously in place at the hospital. Specific to insomnia, patients on the ED program were treated pharmaceutically, mainly with Trazodone (a serotonin reuptake inhibitor/antagonist). On the IMED program, insomnia was treated first via instructions on sleep hygiene, and then, if needed, an herbal product (containing Valerian root extract, Rhodiola rosea root extract, Hops strobiles extract, Passion flower aerial parts extract, and German chamomile flower extract) and/or 5-hydroxytryptophan (the metabolic precursor to serotonin) were prescribed. If these approaches were not successful, patients were prescribed conventional medications for sleep.

Regarding constipation, patients on the ED program were usually given Colace (a stool softener) and/or Metamucil (a bulk-producing laxative). On the IMED program, plant-based digestive enzymes at mealtimes and a daily probiotic supplement containing *Lactobacillus rhamnosus* were given to almost all patients on admission to promote overall digestive health and to prevent the GI problems commonly experienced upon refeeding. If patients still reported constipation they were prescribed conventional constipation medications.

Outcomes

Data were collected via chart review from three types of forms kept in all patients' medical charts. Daily patient reports of having "slept well" and of constipation were gathered from the Daily Patient Feeling Sheets. The actual medications used each 24-hour period were gathered from the routine and PRN (*pro re nada* or "when necessary") medication administration records. Reported admission levels of constipation/diarrhea and insomnia, constipation and sleep medication use, and patient sex and age were gathered from the patient intake reports.

Data analysis

Comparisons of patient characteristics at intake were made using χ^2 for frequency data and *t*-tests for the continuous variables. Because patients had between 29 and 81 days of patient report and medication record data available, two types of analysis were performed to determine differences across groups. Reports of insomnia and constipation and records of medication use for each were first analyzed by comparing the proportion of each patient's stay in which these reports were made or medication used. Averages of these percentages across patients in each group were compared using two-tailed *t* tests.

The second way these data were analyzed was using hierarchical linear modeling (HLM). HLM is a regression-based approach that allows use of nested data (in this case daily

observations for the duration of each patient's stay) by adjusting the error structure to account for the fact that repeated measures on an individual cannot be assumed to be independent.(11.) HLM is also robust to missing data and unbalanced designs. In addition, using HLM allowed determination of whether there was a trend effect during a patient's stay (e.g., they slept better as their stay progressed—particularly important here because on average the IMED cohort had longer stays) and allowed correction for differences seen in patient characteristics at intake (important because patients were not randomized). A separate model was estimated for each outcome variable. The best error structure and best model in each case were determined using a model-level χ^2 test calculated as the difference between each model's deviance statistics.(11.) Basically, if a simpler model (i.e., fewer variables or a simpler error structure) could explain the same amount of variance (i.e., no statistical significant difference in the amount of variance explained), the simpler model was chosen. Following the approach recommended by Raudenbush and Bryk (2002)(11.), the unconditional model was fit first. Then group status was added as an explanatory variable for both the intercept and the time-slope. Finally, patients' baseline characteristics were added. The time variable was centered (i.e., set to zero) for each patient at mid-stay so that the intercept and coefficient for the IMED program indicate average values during each patient's stay.(12-14.) The models were estimated using restricted (residual) maximum likelihood (REML) estimation in the PROC MIXED procedure of SAS for Windows, Version 9.1 (SAS Institute Inc., Cary, NC). The other calculations were made using Microsoft® Office Excel 2003 (Microsoft Corporation, Redmond, WA)

RESULTS

A total of 27 patients were admitted into the eating disorders program from June 1 through November 30, 2004 (the ED group), and 38 patients were admitted during the same time period in 2005 (the IMED group). Table 1 shows the patient characteristics at intake for each group. In general, the two groups are evenly matched at intake. The two sleep measures were taken from different sections of the intake form, and because no further detail is available, both are reported. The IMED cohort had on average significantly longer patient stays, and more variation in the length of stays than the ED cohort. This difference was secondary to a 2005 change in hospital policy that increased the minimum length of stay for patients in the eating disorders program from 30 to 45 days.

The larger number of patients and the longer average patient stays resulted in the IMED group having almost twice the number of individual data points (daily reports or records across all patients or patient-days) than were available in the ED group. The 27 patients in the ED group had among them a total of 845 patient-days, and the IMED group had a total of 1,543 patient-days. Table 2 shows the counts (and percentages) for each outcome variable across patient-days. Two versions of the 'slept well' variable are shown to account for the fact that many patients reported 'slept well' on the same day they also reported 'difficulty falling asleep' or 'early waking'. Two versions of the use of medication for sleep are also shown. The first (use of conventional medication for sleep) includes the use of any pharmaceutical medication where sleep or insomnia was recorded

as its indication for use. The second definition (use of conventional sleep medication) only included the use of medications conventionally used for sleep (e.g., trazodone, zolpidem, diphenhydramine, and hydroxyzine). For all medications, single or multiple dosing in one 24-hour period of the same or different medications of the same type (sleep or constipation) is counted as the use of the medication for one patient-day.

Table 3 shows the results of the direct comparison of the mean percent of days during each patient's stay in which having slept well and constipation was reported and conventional sleep or constipation medications were recorded as having been used. As can be seen, patients in each group were equally likely to report having slept well. However, the recorded use of conventional sleep medications was significantly less in the IMED group—an average of 58% or 50% of days during each ED patient's stay vs. an average of 10% or 7% of IMED patient stays depending on the definition used regarding sleep medication. The number of reports of constipation was also lower on the IMED program, approximately one-third the level seen on the ED program, and the use of conventional medications for constipation was dramatically lower—an average of 15% of each patient's stay (ED) vs. an average of 2% (IMED).

The counts shown in Table 2 are not directly comparable between groups, because multiple measures over time (daily data) on the same individual cannot be assumed to be independent. Therefore, the standard statistical tests are not valid. Tables 4 and 5 show the results of the HLM analyses across patient-days corrected for this lack of independence in observations. Only the best model in each case is reported. A first-order autoregressive structure was the best error structure for all models. Also, neither patient baseline characteristics nor the interaction between group status and the time slope added significant explanatory power to any of the models. Therefore, either the two groups of patients did not differ significantly at baseline (intake) or we did not measure the characteristics by which they differed. Also, the IMED program did not seem to have any effect on any trend seen across patient stays in any of these outcomes.

As can be seen in Table 4, and consistent with the analyses shown in Table 3, there was no significant difference between the IMED and the ED groups in reports of 'slept well' whether this report was given by itself (slept well – only) or in combination with 'early waking' or 'difficulty falling asleep' (slept well – all). In Table 4 this lack of statistical significance is indicated by the IMED group variable not being included in the final model (i.e., the coefficient estimate for IMED group was not significantly different than zero). In both cases the best model included an intercept and a time-related slope for each participant. Because the time variable was centered at mid-stay, the intercept coefficient can be interpreted as the average percent of days over the average patient's stay (across both groups) with a report of slept well. As can be seen, these coefficients are consistent with the averages seen for both groups in Table 3. The positive time slope coefficient indicates that on average across patient stays reports of slept well increased slightly. For reports of constipation, the coefficient for IMED group status had a low *p*-value (0.028), and the model's explanatory power increased when the IMED variable was included in the model. However, the inclusion of this variable did not increase the model's explanatory power by an amount that was statistically significant (*p* value for the

χ^2 test comparing this model to one with only intercept and slope = 0.168). Therefore, it was not included in the final model. This result is consistent with the borderline-significant difference seen in for reports of constipation (p=0.0584) shown in Table 3. The negative time slope coefficient in the constipation model indicates that on average across patient stays reports of constipation were lower in the IMED group vs. the ED group.

Table 5 shows the results of the HLM models for conventional medication use. As can be seen by the negative coefficient estimates for IMED group status, patients in the IMED group had significantly fewer days during their stay where prescription medications were used. Again, these results are comparable to the those seen in Table 3—the intercept coefficient estimates correspond to the averages shown in Table 3 for the ED group and the sum of the intercept and IMED coefficients correspond to the averages shown for the IMED group in Table 3. The negative coefficient on the time slope variable for medications given with the indication of insomnia or sleep indicates that the use of these medications was slightly reduced over the average patient's stay. For constipation medications, the coefficient for IMED group status had a low p-value (0.015), and that variable's inclusion in the model increased its explanatory power. However, the increase in explanatory power was not statistically significant (p value for the χ^2 test = 0.584). Therefore, IMED group status was not included in the final (best) model. In contrast to the significant difference seen between groups when comparing patient-level averages across stays (Table 3), this result indicates that when trying to also account for the variation seen both across days and across patients in constipation medication use, IMED group status does not contribute significant explanatory power.

CONCLUSIONS

The comparison of reports of sleeping well did not differ between the 6-month cohort of patients on the IMED program and those on the previous ED program, but the use of conventional sleep medications did. Recorded patient use of conventional sleep medications in the ED group was about or just over 50% of patient-days vs. 10% or less of patient-days in the IMED group depending on the definition used for sleep medications and the analysis performed. Therefore, IMED patients reported sleeping just as well as their ED counterparts while using conventional medication for sleep one-fifth as often.

Reports of constipation and the use of conventional medications for constipation were both substantially lower on the IMED program vs. the ED program—15% vs. 5% for reports and 15% vs. 2% for medication use. Although these differences can be considered clinically significant, depending on the approach used to analyze these data, they may not be statistically significant. It is most likely that this study lacked the power needed to show a statistical difference in constipation report and medication use because of the large variability in these measures across patients and across patient-days. Post hoc power analyses indicate power of 54% for patient reports and 63% for medication use.

Because of its real world setting and lack of ability to randomize patients into groups, this study used a quasi-experimental design. Whereas potential threats to the validity of a study's conclusions must be addressed even when randomization is possible, the likelihood of these threats and the need to address them is higher in quasi-experimental studies.(15.) One threat to validity (statistical power) has already been addressed above. Other threats of importance for this study include that the two patient groups differed by more than the treatment received (e.g., different types of patients were admitted to the eating disorders program during the two periods), that basic patient care at the hospital had changed significantly between the two time periods, and that patient reports differed systematically between groups for reasons other than differences in patient care. Regarding a basic difference in the two patient groups, a comparison of patient characteristics at intake (Table 1) shows that they are roughly similar. However, it is possible that these patient groups differed by important variables (i.e., variables related to their outcomes) not measured in this study. Regarding changes in basic patient care, a review of hospital policy documents and interviews with key staff whose tenures covered and bridged both periods indicate no evidence of changes in basic hospital care (e.g., the types and quality of the food served in the cafeteria or general hospital policy on medication use) that could account for changes in insomnia and constipation reports and medication use. Finally, regarding changes in reporting documents and their administration, the reporting documents used for both cohorts were identical, their administration is routine, and this routine was unchanged between groups.

In the Methods section above, the IMED intervention is described as an herbal or nutraceutical medication for insomnia and digestive enzymes and Lactobacillus for constipation. It is possible, however, that other components of each cohort's eating disorders program may have contributed to the changes seen in insomnia and constipation reports and medication use. The previous (ED) program can be said to represent standard of inpatient care for eating disorder treatment. It consisted of group and individual psychotherapy, routine medical/psychiatric care, meal monitoring, equine therapy, recreational therapy and treatment of co-occurring diagnoses such as substance abuse, major depression and other mood disorders, and trauma. It did go, however, beyond usual standard of care in that patients were able to receive acupuncture, massage, chiropractic care, and Shiatsu. The IMED program differed from the previous ED program in several ways in addition to the use of the supplements described. These differences include a newly instituted levels structure that outlined specific, measurable behaviors patients needed to complete before advancing to the next level (to increase patient autonomy); eating disorder skills training (including mindfulness training) based on the principles of Dialectical Behavioral Therapy (DBT); a stronger team approach including team case conferences, weekly team meetings, and frequent team-wide email communication to present more of a "united front" to patients; a fully dedicated nutritionist; a full nutraceutical regimen including essential fatty acids, full multivitamin/mineral supplementation, and nutritional and herbal support for mood, insomnia, and digestion; and additional (e.g., Reiki and Zero Balancing) and more access to all integrative therapies.

In conclusion, the results of this retrospective study suggest that patients with eating disorders benefit from integrative medicine interventions in terms of reduced need for conventional medications for sleep and reduced constipation and need for conventional constipation medication. Although neither insomnia nor constipation are central to these patients' pathologies, both can be distracting to recovery and conventional treatments can be troublesome. Integrative medicine interventions can provide effective alternative treatments making more energy and attention available to devote to the work of recovery and reducing barriers to refeeding.

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Table(s)

Table 1. Patient characteristics at intake; number (%) unless indicated otherwise

Variable	ED Program (n=27)	IMED Program (n=38)	*p*-value for Difference
Female	25 (93)	34 (89)	0.669
Average age (SD)	28.7 (10.3)	28.6 (10.3)	0.959
Sleep poorly	19 (70)	23 (61)	0.413
Difficulty sleeping	15 (56)	16 (42)	0.285
Constipation/diarrhea	10 (37)	16 (42)	0.681
Sleep medication	7 (26)	4 (11)	0.103
Constipation medication	2 (7)	0 (0)	0.088
Average stay (SD)	31.3 (3.6)	40.6 (12.2)	0.0001

Table 2. Total number (%) reports of insomnia and constipation and records of sleep and constipation medication use by group

Number of:	ED Program (n=27 patients; N=845 patient-days)	IMED Program (n=38 patients; N=1543 patient-days)
Reports of 'slept well' only*	577 (68)	985 (64)
Reports of 'slept well' all**	651 (71)	1166 (76)
Reports of constipation	127 (15)	83 (5)
Use of conventional medication for sleep	490 (58)	182 (12)
Use of conventional sleep medication	422 (50)	114 (7)
Use of conventional constipation medication	133 (16)	47 (3)

* Only included reports of 'slept well' that were not accompanied by reports of 'difficulty falling asleep' or 'early waking'.
** Included all reports of 'slept well'.

Table 3. Comparison between groups of the average percent of each patient's stay that included reports of having slept well and of constipation and records of medication use for sleep and constipation; Mean (SD)

Average proportions of each patient stay:	ED Program (n=27 patients)	IMED Program (n=38 patients)	*p*-value for *t* Test of Difference

Reports of 'slept well' only*	68 (7)	64 (9)	0.570
Reports of 'slept well' all**	77 (4)	74 (7)	0.570
Reports of constipation	15 (6)	5 (1)	0.058
Use of conventional medication for sleep	58 (12)	10 (6)	<0.0001
Use of conventional sleep medication	50 (13)	7 (4)	<0.0001
Use of conventional constipation medication	15 (9)	2 (1)	0.037

* Only included reports of 'slept well' that were not accompanied by reports of 'difficulty falling asleep' or 'early waking'.
** Included all reports of 'slept well'.

Table 4. Hierarchical linear model results for reports of 'slept well' and constipation

	Dependent variable					
	Slept well – only		Slept well – all		Constipation	
Independent variables	Estimate	*p*-value	Estimate	*p*-value	Estimate	*p*-value
Intercept	0.663	<.0001	0.758	<.0001	0.088	0.0002
IMED group	-	-	-	-	-	-
Time slope	0.005	0.0005	0.005	<.0001	-0.003	<.0001

Table 5. Hierarchical linear model (HLM) results for conventional medication use for insomnia and constipation

	Dependent variable					
	Medications used for sleep		Sleep medications		Constipation medications	
Independent variables	Estimate	*p* value	Estimate	*p* value	Estimate	*p* value
Intercept	0.564	<.0001	0.485	<.0001	0.071	0.006
IMED	-0.463	<.0001	-0.420	<.0001	-	-
Time slope	-0.003	0.030	-	-	-	-

*** Cover Letter**

Carolyn C. Ross, MD, MPH
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Dear Editor:

I am submitting for your review attached manuscript entitled: *Evaluation of Integrative Medicine Supplements for Mitigation of Chronic Insomnia and Constipation in an Inpatient Eating Disorders Setting.*

This manuscript represents original research, the first of its kind to evaluate the use of nutraceuticals to treat insomnia and digestive complaints in this difficult to treat population of patients with eating disorders.

Sincerely,

Carolyn C. Ross, MD, MPH