

Pitfalls in Migraine Diagnosis and Management

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The decade of the 90s brought about a revolution in our understanding of migraine and in medications to treat this disorder. Indeed, our understanding of the pathophysiology of migraine and the pharmacology involved in its treatment has exploded. Nonetheless, there are still many pitfalls that may occur in the clinical assessment and management of migraine that may prevent the patient from receiving the full benefits of the advances of the past 10 years. This article explores the reasons for the unsuccessful diagnosis and treatment of migraine and presents suggestions for improving its management.

All too often the correct clinical diagnosis of migraine for one reason or another is not made. Furthermore, even when the correct diagnosis is reached, adequate treatment is not always initiated quickly or efficiently, which leads to unnecessary suffering and may even cause patients to lapse from care. Sometimes when appropriate therapy is initiated there may be problems with drug interactions or medication-induced headaches. Also, inappropriate patient selection, ie, treating patients with headache medications who have other medical conditions such as coronary risks, continues to be a concern. With effective physician and patient education, these and other pitfalls in migraine diagnosis and management can be avoided.

THE MISDIAGNOSIS OF MIGRAINE

In 1989 there were ~24 million migraineurs in the United States. Ten years later, surveys showed that the prevalence of migraine in the general population had increased to 28 million persons (1). These data also indicated that 1 of every 4 households had a migraine sufferer. Furthermore, 90% of patients

KEY POINT

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with migraine considered their attacks to be at least moderate or severe. It has now been estimated that migraine is responsible for annual direct health expenditures of ~\$1 billion per year and ~\$13 billion of lost productivity and 112 million bedridden days per year (2). Clearly, the societal and economic burdens of migraine are greater than ever, yet physician-diagnosed migraine has increased only modestly—from 39% to 48% over the past 10 years (3).

There are several reasons for the unfortunate lack of successful migraine diagnoses and they relate to biases, misinformation, and the lack of

effective education of both physicians and patients. Many medical education programs have missed the mark when it comes to updating physicians, medical students, and other health professionals on the diagnosis of migraine and the appropriate use of new therapeutic agents for its treatment (4). In addition, many migraine sufferers have low expectations about achieving good control of their headaches. Often, they have been led to believe by medical practitioners and lay people alike that migraine is not a legitimate medical disorder but a symptom of poor self-control. Furthermore, they come to know that the disorder is episodic and not life-threatening, and there are no objective tests to confirm its diagnosis. As a result, they believe their illness cannot be understood and become discouraged and lapse from care or never present to the clinic in the first place. To make matters worse, because most migraineurs have relatives who also have a history of severe, difficult headaches, they mistakenly believe they have a family legacy or “curse” for which there is no effective treatment. So they believe they must live a life of suffering similar to that of other family members and never seek medical care for their headaches.

The most common misdiagnosis is sinus headache (2). Physicians and patients alike misinterpret frontal, maxillary, or periorbital pain to be a paranasal sinus infection, obstruction, or inflammation. Although sinus disease may be associated with face and head pain, it is a relatively uncommon cause of significant headache pain. When a sinus etiology of pain is present, it is usually due to infection, and the patient will most often experience fever, purulent nasal discharge and postnasal drip, and other upper respiratory symptoms. When these signs and symptoms are absent, the likelihood of sinus infection as the etiology of headache is actually quite low. Furthermore, sinus infection is usually associated with erythema of the nasal membranes, which may be seen on inspection of the nasal passages. If the nasal mucosa is pale or pink on inspection, the patient probably does not have significant sinus disease. Limited computed tomography (CT) of the sinuses is probably the best way to evaluate the sinuses radiographically. The absence of significant fluid levels or obstruction on the CT

scan should effectively rule out sinus disease as a cause of significant head or face pain.

Many patients with migraine erroneously presume they are suffering with sinus headache and treat it with over-the-counter decongestants and analgesics, which afford only temporary relief, thereby lending some credence to their suspicions regarding their symptoms. One study showed that as many as 97% of patients with self-diagnosed sinus headache actually have migraine and they frequently respond well to treatment with migraine-specific therapy (5). A better understanding of the clinical presentation of migraine therefore will lead to improvement in its diagnosis.

Tension headache is another common misdiagnosis that leads to inadequate or inappropriate treatment and lapses in patient care. Migraine may present with significant cervicgia and tension in the muscles of the neck, shoulders, and upper back. Sometimes patients and clinicians construe these musculoskeletal manifestations as being consistent with only tension headache. This incorrect assumption may easily lead to unsatisfactory treatment and risk of lapse from care.

Another factor that makes the diagnosis of migraine difficult may be the primary headache diagnostic criteria themselves. In 1988, the International Headache Society (IHS) published classification guidelines for primary headache types (**Tables I, II**). These guidelines have been instrumental in defining headache types and in standardizing research that has made possible the development of new drugs for treating migraine. The IHS criteria however are not always useful in clinical practice. Simply put, these criteria are highly specific and not very sensitive. Many migraine headaches may not fit the diagnostic criteria, yet still have migraine physiology and respond to migraine-specific therapy. If clinicians adhere too stringently to the IHS criteria, they may misdiagnose. Additionally, overlapping symptoms, such as migraine with steady, pressing pain only or tension-type headache with photophobia, may make diagnosis difficult.

Many clinicians may find it helpful to use a “default diagnosis” process, particularly when a patient has a long-standing headache syndrome

TABLE I.

IHS CLASSIFICATION GUIDELINES FOR MIGRAINE

- **1.1 Migraine without Aura**
 - At least 5 attacks with at least 2 of the following
 - Unilateral
 - Pulsating
 - Moderate to severe intensity
 - Physical activity aggravates
 - At least 1 of the following
 - Nausea and/or vomiting
 - Photophobia and phonophobia
 - No organic disease
- **1.2 Migraine with Aura**
 - At least 2 attacks with at least 3 of these 4 items
 - One or more fully reversible aura symptoms indicating brain dysfunction
 - At least 1 aura symptom develops gradually over more than 4 minutes or 2 or more symptoms occur in succession
 - No single aura symptom lasts more than 30 minutes
 - Headache follows aura with a free interval of less than 60 minutes
 - No organic disease
- **1.7 Migrainous**
 - Does not fulfill all of the above criteria

with intermittent severe attacks. In this situation the physician would consider migraine as the primary diagnosis unless another ailment is suspected due to a worrisome history or abnormal physical examination. Accordingly, rather than using the IHS guidelines, a more practical way to diagnose migraine in a primary care setting may be to use a shorter, more inclusive screening tool such as the Brief Headache Screen (**Table III**). This instrument allows the clinician to zero in on a diagnosis of migraine by focusing on the impact of the headache syndrome, presuming that a chronic, intermittently disabling headache syndrome is likely to be migraine. At the same time, this screening tool allows the clinician to efficiently rule in or out analgesic overuse syndrome.

INADEQUATE TREATMENT

Because migraine is considered a functional, non-life-threatening condition, many primary care clinicians and even neurologists have not given it high priority in their effort to stay current on the multitude of medical conditions they face in day-to-day practice. As a result, they may be unaware of the newer insights into migraine pathophysiology and pharmacotherapy. It is also true that physicians who are up to date with these newer precepts may not necessarily put them to use. Biases and fears about medications, cost concerns, inadequate knowl-

KEY POINT

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Why do physicians prescribe the way they do? The answer to this question may never be found. However, a look at some aspects of prescribing habits and biases will help to illuminate some reasons why patients receive inadequate treatment. Physicians prescribe medications they are familiar with or have a great deal of experience in using. Breaking this paradigm of prescription selection is very difficult and should be initiated by the physician. With the time constraints and the pressures of extensive administrative demands common in clinical practice today, physicians find

TABLE II.

IHS CLASSIFICATION GUIDELINES FOR TENSION-TYPE HEADACHE

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|---|---|
| <ul style="list-style-type: none"> ● 2.1 Episodic – At least 10 headaches lasting from 30 minutes to 7 days with at least 2 of the following <ul style="list-style-type: none"> ● Pressing, tightening, nonpulsatile ● Mild or moderate intensity (may inhibit but not prohibit activity) ● Bilateral location ● Not aggravated by routine physical activity – In addition <ul style="list-style-type: none"> ● No nausea or vomiting ● Photophobia or phonophobia may be present, but not both | <ul style="list-style-type: none"> ● 2.2 Chronic – Headache occurred 15 or more days/month for 6 months – Pain described by 2 of the following <ul style="list-style-type: none"> ● Pressing, tightening quality ● Mild or moderate intensity (may inhibit but not prohibit activity) ● Bilateral location ● Not aggravated by routine physical activity – In addition <ul style="list-style-type: none"> ● No vomiting ● No more than 1 of the following: nausea, phonophobia, or photophobia |
|---|---|

themselves unable to spend the time necessary to become comfortable with new pharmacotherapeutic agents, especially for the treatment of non-life-threatening illnesses. When the degree of disability associated with migraine attacks is brought to their attention, clinicians tend to be more aggressive with their treatment regimens and to use migraine-specific therapy more readily.

Medical schools and graduate medical education programs have not adequately emphasized the diagnosis and treatment of primary headache over the past 10 years. As a result, even new physicians who are recently trained have not received adequate instruction regarding the pathophysiology and pharmacology of migraine. They are no less at a disadvantage than experienced clinicians who have not kept up to date with the subspecialty medical literature.

Many researchers and thought leaders in the field of headache would like to see a greater emphasis on primary headache in the medical education curriculum, which would help ensure that future graduates have a greater understanding of the prevalence and burden of headache and thus improve their treatment of migraine. In the meantime, continuing medical education programs and other educational efforts should emphasize primary headache disorders as chronic, legitimate medical



KEY POINT

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conditions that can be understood and treated adequately to decrease disability and improve quality of life.

DRUG INTERACTIONS

The prevalence of polypharmacy among migraine sufferers is about 79% because many migraineurs have a need for both acute and prophylactic medications as well as treatment for comorbid conditions such as depression, anxiety, irritable bowel syndrome, and fibromyalgia (6). As is the case with all classes of medications, the migraine-specific agents—the 5-hydroxytryptamine₁ (5-HT₁) receptor agonists or triptans—carry the potential for drug interactions that prescribers need to understand.

Drug interactions fall into 2 categories: pharmacodynamic (changes in the effects on the body)

TABLE III.

IMPACT-BASED RECOGNITION OF MIGRAINE

- How do headaches interfere with your life?
- How frequently do you experience headaches of any type?
- Has there been any change in your headache pattern over the last 6 months?
- How often and how effectively do you use medication to treat headaches?

and pharmacokinetic (changes in the way the drug is handled in the body). For most drugs that are used intermittently, the pharmacodynamic interactions are usually the most important. For the triptan class of drugs, this pertains to the use of the medications concomitantly with other vasoconstrictors. A theoretical concern exists that there may be additive effects of vasoconstriction when triptans are used together with ergot derivatives or with other triptans. Reliable evidence to refute these concerns does not exist, so these combinations remain contraindicated.

Alterations in the pharmacokinetics of triptans when taken with other medications are relatively uncommon, but a few potential interactions deserve mention as they can represent a pitfall in the treatment of migraine if unheeded. The oral triptans, which are metabolized by the monoamine oxidase (MAO) pathway, should not be administered together with MAO inhibitors. The marketed triptans that may accumulate to high blood concentrations under these circumstances include sumatriptan, zolmitriptan, and rizatriptan. A special situation exists in the coadministration of these same triptans with propranolol, which shares with them the MAO-A pathway. Studies show a pharmacokinetic interaction for each of these medications with propranolol. Of the 3 triptans, only rizatriptan has a propranolol interaction significant enough to warrant a change in dosage—this agent has a 70% increase in the area under the curve when given with propranolol (7–9). When rizatriptan is given to patients taking propranolol, the dose should be reduced from 10 mg to 5 mg. It is important to note that this interaction applies only to propranolol and not to other β -adrenergic blockers. Also important is that in none of the studies was there any evidence of pharmacodynamic interaction.

Interactions involving drugs metabolized via the cytochrome P-450 system present problems when these agents are combined with macrolide antibiotics and antifungal agents, among others. None of the currently marketed triptan drugs are metabolized solely by a single cytochrome P-450 enzyme. Naratriptan is metabolized by numerous enzyme subtypes within the cytochrome system. As a result, the drug has many avenues of metabolism that may be utilized should one enzyme subtype become inhibited. Accordingly, no significant pharmacokinetic drug interactions occur with naratriptan. Only about 12% of almotriptan is metabolized by the cytochrome P-450 system, accounting for only a small portion of the drug's metabolism, and there are no significant problems with other drugs metabolized in the cytochrome system. One step of the metabolism of zolmitriptan is carried out predominantly by the cytochrome P-450 subtype 1A2, which can be associated with an interaction with cimetidine (10). Although this interaction does not constitute a contraindication, caution is warranted when the 2 drugs are combined (**Table IV**).

Another potential interaction that has received considerable attention is the combination of triptans with selective serotonin reuptake inhibitors (SSRIs). Because the triptans trace their mechanism of action to the agonism of certain subtypes of serotonin receptors, it has been theorized that a potentiation of the effects of the triptans may be possible when combined with SSRIs. Indeed, a few cases of the so-called serotonin syndrome—eg, ataxia, irritability, and hyperreflexia—have been described in the literature. Other than these isolated reports of this possibly overlooked syndrome, clinicians have not had a reasonable idea of its prevalence. Putnam and colleagues published study results in 1999 that evaluated migraine sufferers who used sumatriptan

TABLE IV.

TRIPTANS: DRUG INTERACTIONS

	<i>Monoamine Oxidase Inhibitors</i>	<i>Cimetidine*</i>	<i>Propranolol†</i>
Sumatriptan (Imitrex®)	✓		
Zolmitriptan (Zomig®)	✓	✓	
Naratriptan (Amerge®)			
Rizatriptan (Maxalt®)	✓		✓
Almotriptan (Axert®)	✓ (minimal)		

* The half-life and area under the curve of zolmitriptan and its active metabolites are ~doubled following administration of cimetidine.

† Rizatriptan 5 mg should be used in patients taking propranolol as propranolol has been shown to increase the plasma concentrations of rizatriptan by 70%.

Note: See package inserts.

injection for the treatment of migraine for 1 year (6). In this population of patients, 1784 were also taking SSRIs as well. The incidence of central nervous system side effects of any kind was only 0.8%. These figures point to the relative rarity of this syndrome. Although clearly a condition of which clinicians should be aware, serotonin syndrome does not occur with significant frequency with the use of triptans and certainly does not constitute a true contraindication for the concomitant use of SSRIs.

MEDICATION OVERUSE AND THE ANALGESIC REBOUND SYNDROME

Perhaps one of the greatest pitfalls of the management of migraine is symptomatic medication overuse, which may lead to habituation (in the case of narcotics or barbiturates) or analgesic rebound syndrome, or both. The latter situation deserves special consideration because of its increasing prevalence. It is estimated that 30% to 75% of headache sufferers who present to specialty clinics have chronic daily headache with medication overuse (11). Through changes in serotonin blood levels and plasticity of serotonin and opioid receptors over the course of recurrent and frequent analgesic use (prescription or over-the-counter), patients develop a progressive syndrome of more frequent, prolonged headaches to the point where they have chronic daily headache. With persistent

KEY POINT

It is estimated that 30% to 75% of headache sufferers who present to specialty clinics have chronic daily headache with medication overuse.

medication use, the headaches become refractory to any type of treatment and require escalating doses of analgesics for the patient to have even partial symptom relief. Furthermore, patients find this scenario does not respond to the implementation of prophylactic medication regimens. Those patients suffering from analgesic overuse syndrome will have a chance of finding relief only if they discontinue the offending medication for ~12 weeks, the estimated time necessary for the serotonin levels and receptor populations to normalize.

The initial medication withdrawal period can be difficult, and many patients are not willing to stop the offending medications, at least initially. However, once a patient understands the hopelessness of the situation, that patient usually will participate in a detoxification program. Often, bridging regimens, which are designed to soften the blow of the initial withdrawal period, may assist analgesic rebound sufferers. A few successful bridging programs are presented in

TABLE V.

DETOXIFICATION FROM REBOUND HEADACHES (SUPPORT AFTER CESSATION OF ANALGESICS)

- Medrol® Dosepak™ or Kenalog 40 mg IM × 1
- Sumatriptan 25 mg po tid × 10d
- Tizanidine 2 to 4 mg hs and a long-acting NSAID (rofecoxib, celecoxib, ketoprofen SR, or piroxicam) po qd × 12 wk

NSAID = nonsteroidal anti-inflammatory drug.

the recent medical literature, including a short course of tapering steroids (12); as many as 10 days of repetitive triptan use, followed by as-required use only (13); and daily use of *tizanidine hydrochloride** in combination with a long-acting nonsteroidal anti-inflammatory drug (NSAID) to be taken through the 12 weeks of withdrawal (14) (Table V).

In each of these treatment schemes the true reason for response is the cessation of the offending medication. The added pharmacotherapeutic agents merely enable a patient to successfully stop the symptomatic medication that has been taken to excess. Although prophylactic medications may not have an initial effect, it is generally believed wise to start them early to give the patient better support as treatment proceeds. During the detoxification period, analgesics must be avoided to prevent relapse into further rebound headache attacks. Physicians generally may treat significant headache attacks with triptan drugs or dihydroergotamine (DHE) as long as these agents are not overused themselves. If patients are suspected of rebounding to triptan medications, they should be treated with DHE alone. If all else fails, hospitalization for around-the-clock administration of IV DHE may be helpful in getting through the first few days. Obviously, when appropriate and available, consultation with a neurologist or headache specialist with experience in treating this syndrome can be invaluable. In extreme cases, referral to a tertiary center for intense therapy may be warranted.

CONTRAINDICATIONS AND WARNINGS

A potentially serious pitfall in the management of

* Use not FDA approved for the treatment of migraine headache.

KEY POINT

Clinicians should avoid prescribing any vasoconstrictors—including triptans—for patients with risk factors for or a history of coronary disease. Triptans also should not be used by patients who have poorly controlled hypertension, cerebrovascular disease, or peripheral vascular disease.

migraine is the use of triptans or other vasoconstrictors by patients for whom they are not appropriate. The triptans have relative cerebroselectivity with regard to their vasoconstrictive effects, which are due to their action on the 5-HT_{1B} receptors. However, there may be some minor overlap effect on the 5-HT₂ receptors in the coronary arteries, causing vasoconstriction. This vascular effect of triptans would be clinically significant only in a patient with underlying coronary disease or variant angina. For this reason, clinicians should avoid prescribing any vasoconstrictors for a patient with a history of or risk factors for coronary disease. Fortunately, when triptans are used wisely, serious adverse events are extremely rare.

For similar reasons, triptans should not be used by a migraine patient who also has poorly controlled hypertension, cerebrovascular disease, or peripheral vascular disease. However, treatment with triptans may be appropriate if a patient has acceptable blood pressure control with antihypertensive medication. Triptans are further contraindicated in patients with complicated migraines such as hemiplegic, basilar, or ophthalmoplegic variants,

although these forms of migraine are uncommon. Physicians should have an awareness of these complicated migraine variants to assure that inappropriate treatment is not prescribed.

Lastly, triptans are currently contraindicated for use during pregnancy and lactation. All of the pharmaceutical manufacturers of triptans have established a pregnancy registry to gather information on the outcomes of pregnancies in which the mother experiences incidental or accidental exposure to a triptan drug. The database of pregnancy outcomes is still relatively small, but no clear-cut teratogenic effects have yet been noted. Further study documentation is needed before any conclusions may be drawn from these data.

SUMMARY

The diagnosis and management of migraine need not be fraught with difficulty. However, pitfalls exist that can impede a successful approach to migraine care for even the most careful physician. These pitfalls include misdiagnosis, inadequate treatment, drug interactions, development of the analgesic rebound syndrome, and poor patient selection when treating with vasoconstrictor therapy. Most of the shortcomings in these areas can be overcome through better educational efforts for both physicians and patients.

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Dialogue Box

ADVISORY BOARD

Of the nontricyclic antidepressants—that is, the SSRIs *venlafaxine, *nefazodone**, *mirtazapine**, *bupropion**—which do you favor in the migraineur who uses a triptan agent?**

SMITH

In general, I do not find the SSRIs as useful for migraine prophylaxis as the tricyclics. If patients have comorbid depression, they can be helpful. Some of the newer antidepressants have been studied with mixed results, including nefazodone and venlafaxine.

ADVISORY BOARD

What clinical characteristics or clues should alert the clinician of a high likelihood that migraine is responsible for the symptoms in a patient with self-diagnosed sinus headache?

SMITH

I would look at a few distinguishing characteristics. Migraine is more likely to be severe and accompanied by nausea (although not always). More important is the fact that true sinus-related pain is usually accompanied by fever and/or purulent nasal discharge. Location of the pain is not an identifying hallmark for either.

ADVISORY BOARD

Is there a role for a diagnostic trial with a triptan agent to assess the likelihood of migraine causing the symptoms in a patient with a self-diagnosed sinus or tension-type headache?

SMITH

Because there are reports of triptans partially relieving pain from other etiologies, I would stop short of recommending a true diagnostic trial of a triptan. On the other hand, it is certainly reassuring

and confirmatory when a patient with suspected underlying migraine responds well. Also, lack of response to a triptan does not necessarily rule out migraine as the diagnosis.

ADVISORY BOARD

Please elaborate on the role and use of steroids in patients with recalcitrant or status migraine?

SMITH

A brief burst of corticosteroids can be very helpful to “break the cycle” of a recalcitrant headache. If migraine or migrainous headache has persisted beyond 3 days, it is a reasonable consideration if there are no contraindications. I use triamcinolone 40 mg IM or methylprednisolone (MEDROL[®] DOSEPAK[™]) rapid taper over 6 days.

ADVISORY BOARD

Please comment on the use of steroids in patients with analgesic rebound headache.

SMITH

The use of corticosteroids in patients with analgesic rebound is adjunctive and similar to that outlined for status migraine above. The intent is to suppress the headache as much as possible during the problematic first few days to a week after discontinuing analgesics.

ADVISORY BOARD

What is the rationale behind the use of tizanidine in patients with analgesic rebound headache and how is it best prescribed?

SMITH

Tizanidine is useful due to its skeletal muscle relaxant effects, its sedative effects which may

**Use not FDA approved for migraine prophylaxis.*



Dialogue Box

improve sleep, and its antinociceptive properties. It does have α_2 -agonist effects in the upper brainstem including the locus ceruleus, which may have headache prophylactic effects. I use it in low doses at bedtime initially, starting at 2 mg and titrating upward by adding 2 mg every 2 weeks or so. Many times only low doses are required.

ADVISORY BOARD

How successful is the outpatient management of analgesic rebound headache and what specific regimen do you favor?

SMITH

Most reported outpatient programs for analgesic rebound are successful 60% to 75% of the time. Currently I am most often using low-dose nocturnal tizanidine along with a daily long-acting NSAID (such as ketoprofen SR, rofecoxib, or celecoxib). Some patients will also receive corticosteroids as described earlier. All patients are given educational material regarding the nature of rebound headaches, headache risk reduction, and biofeedback.

ADVISORY BOARD

Is there an age above which triptans should not be used or that a formal diagnostic evaluation for the presence of CAD should be undertaken?

SMITH

No, there isn't an age above which triptans should never be given. This decision needs to be individualized. Patients with known CAD or symptoms

suggesting CAD should not be given triptans no matter what age. In patients >50 years of age with ≥ 1 risk factor for CAD, consideration should be given to risk stratification for CAD to include at least a resting electrocardiogram as well as screening for other risk factors (cholesterol, diabetes, etc.). Arguably, their primary care physician should evaluate them for these factors whether they are to receive a triptan or not. Some clinicians give the initial dose of triptan in the office setting for observation and reassurance. Obviously, patients with high risk should have an extensive evaluation such as a stress echocardiogram. The American Headache Society is assembling an expert panel to review these issues and generate a position statement, which may be helpful with this situation in the future.

ADVISORY BOARD

Are there clinical criteria that would favor hospitalization of the analgesic rebound headache patient for treatment?

SMITH

There are no widely accepted criteria per se. Patients with failed attempts at outpatient detoxification programs and patients who are at high risk for complications from medication withdrawal (barbiturate habituation) should be hospitalized for treatment. Other factors would include the presence of comorbid conditions (eg, depression), dehydration and poor oral absorption, and inadequate social support.