"There have been no studies published comparing the newer atypical antipsychotic agents. Such studies would be of value since some of these agents are becoming first-line medications in the treatment of psychotic individuals, and nothing is known regarding direct comparisons of their efficacy. Pharmacological treatment studies directly comparing the various efficacies of atypical antipsychotic agents are much anticipated."

Dear Editor:

Clozapine, an atypical neuroleptic, has demonstrated greater efficacy in treatment of refractory schizophrenia[1] in controlled trials against chlorpromazine and haloperidol.[2] As compared with standard antipsychotic agents, clozapine causes fewer extrapyramidal side effects, and rarely is associated with tardive dyskinesia and neuroleptic malignant syndrome. Clozapine, however, causes significant sedation and orthostasis, and approximately 1% of patients treated with this medication experience agranulocytosis,[3] necessitating regular blood monitoring and, in some cases, discontinuation of the medication. Olanzapine, a newer atypical antipsychotic agent, is a thienobenzodiazepine that has pharmacological effects similar to those of clozapine at dopamine, serotonin, histamine, and muscarinic receptors.[4] Olanzapine, however, has a low affinity for α_2-adrenergic receptors,[5] and is less likely to cause orthostasis and rarely has been associated with agranulocytosis. When given in the usual therapeutic doses, olanzapine has a significantly lower rate of extrapyramidal symptoms than haloperidol.[6,7] No study, however, has directly compared the efficacy of olanzapine with clozapine.

We would like to report a case of a schizophrenic patient who demonstrated greater clinical response to olanzapine than clozapine. Mr. R is a 35-year-old homeless single male with a long history of chronic paranoid schizophrenia and crack cocaine dependency who has had multiple psychiatric hospitalizations. The patient was intermittently compliant with chlorpromazine 200 mg q.d.. Mr. R reported the onset of chronic, unremitting auditory hallucinations at age 9, which preceded his cocaine use by 15 years. Documentation from a prior hospitalization confirmed his assertion that his hallucinations vary in intensity but are always present, even after weeks of inpatient treatment with regular toxicology testing.

The patient was admitted to an acute inpatient unit secondary to command auditory hallucinations demanding he jump onto train tracks and condemnatory auditory hallucinations accompanied by feelings of despair and depression. Urine toxicology on admission was positive for cocaine and Mr. R reported use of approximately $10–20 of crack per day. On admission, and after the acute intoxication passed, the patient showed poor eye contact accompanied by mild psychomotor retardation. His speech was nonspontaneous, monotone, and decreased in volume. Affect was flat, or inappropriately punctuated by smiles when talking about his suicidal ideation/command auditory hallucinations. He remained withdrawn on the unit and did not participate in activities, but rather isolated himself and remained in his bed with the sheets drawn over his head. The Brief Psychiatric Rating Scale (BPRS) score on admission was 81.

Mr. R underwent a trial of chlorpromazine up to 400 mg/day for a period of 4 weeks without change in his behavior and affect, but with increased sedation and blurred vision. He continued to report command auditory hallucinations to commit suicide, and there was no change in his BPRS score. Mr. R did, however, agree that crack use exacerbated his symptoms and expressed interest in applying to mental illness chemical abuse (MICA) residences.

Chlorpromazine was discontinued and Mr. R started on clozapine treatment for the first time. His dose was titrated by 25 mg/day. Mr. R reported a gradual diminution of auditory hallucinations to what he termed tolerable intensity of 3 out of 10 on a relative scale (10 being the worst), as compared with 10 out of 10 on admission. The patient's eye contact improved and affect became less flat but remained blunted, accompanied by inappropriate smiling at times. With continued encouragement, Mr. R's participation in unit activities and interactions with peers began to increase. Because of Mr. R's decreased but remaining command auditory hallucinations and inappropriate affect, clozapine titration was continued up to 600 mg/day. A blood level of clozapine and norclozapine drawn at that time was 620 ng/ml (a therapeutic dose is considered to be greater than 450 ng/ml). Atenolol, 25 mg/day, was added for treatment of tachycardia with good response. Mr. R experienced side effects of sedation, hypersalivation, constipation, and mild dizziness. Orthostatic hypotension was not present. Mr. R was accepted into a MICA program and was discharged. Unfortunately, he did not follow through with this treatment plan. On discharge his BPRS score was 52.

The patient returned to the inpatient unit approximately 5 months after discharge with active crack cocaine use and increased command auditory hallucinations. He did not continue his clozapine after discharge and had been intermittently obtaining chlorpromazine from a walk-in medication clinic. Mr. R was admitted after following command auditory hallucinations

https://doi.org/10.1017/S1092852900005575 Published online by Cambridge University Press

and jumping onto train tracks in order to kill himself. Fortunately, no train was nearby and he was pulled off the tracks by witnesses. Similar to the earlier admission, Mr. R presented with alternating flat and inappropriate affect, depressed mood, and suicidal thoughts. He was withdrawn, stayed in bed all day, and did not show any interest in socializing or participating in groups. On readmission, the patient's BPRS was 78. Mr. R stated that his substance abuse urges overcame him and kept him from following through with placement in the MICA residence. Secondary to prior problems with sedation, compliance, and ambivalence regarding regular blood drawings, Mr. R was started on olanzapine 10 mg p.o. each night rather than clozapine. Within 1 week of treatment, Mr. R started to demonstrate a dramatic improvement: His auditory hallucinations gradually diminished, and after 2 weeks of treatment, they were completely gone. This was the first time Mr. R was free of auditory hallucinations since their onset approximately 26 years prior.

Mr. R showed increased cooperation with medical staff and peers, spending time listening to music and participating in a substance abuse treatment group and other groups. In art therapy, Mr. R drew pictures of flowers and people playing games and gathering together. During his prior hospitalization he had drawn pictures of sharks and anthropomorphic beasts with dismembered and bloody pieces of human bodies inside or around them and had stated, "This is how voices are." Mr. R demonstrated focused and goal-oriented thoughts, his affect was blunted but appropriate, and his mood was euthymic. He went on two successful interviews for MICA programs and failed to return to the hospital for treatment after a third interview. Mr. R's BPRS score around this time was 31.

This case points out some of the many challenges in working with mental illness chemical abuse patients (MICA) patients, and how clinical response to a medication is only a part of the total picture. Our treatment team, however, was quite impressed by the greater efficacy and reduced side-effect profile of olanzapine as compared with clozapine in this specific case. Of course, one cannot make generalizations from a single uncontrolled trial. More recently, olanzapine has been shown to be more effective in the treatment of negative symptoms of schizophrenia and to have greater efficacy in this population than the standard neuroleptic haloperidol,[5] and more cost-effective compared with the other atypical neuroleptics.[8] There have been no studies published comparing the newer atypical antipsychotics agents. Such studies would be of value since some of these agents are becoming first line medications in the treatment of psychotic individuals, and nothing is known regarding direct comparisons of their efficacy. Pharmacological treatment studies directly comparing the various efficacies of atypical antipsychotic agents are much anticipated. CNS

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Dear Editor:

Our parents, natural as well as professional, are typically less dumb than we perceive them to be. McGlashan's article, "Schizophrenia and Obsessive-Compulsive Disorder: Are They Related Disorders?"[1] starts with the point that "older nosological schemes in the field of neuropsychiatry regarded schizophrenia and obsessive-compulsive disorder as mutually exclusive disorders, completely separate and unrelated, with no coexistence between them."[1] Furthermore, "such categorical dogmatism is curious, considering that this 'rule' was totally unfounded by empirical observation."[1] Curious, yes, but even more curious is the fact that this statement is untrue!

Contrary to McGlashan's statements, ▶

"One of our more recent 'parents,' Jaspers, perhaps the principal architect of the 'older nosological schemes,' tried to get around the enmeshment of obsessional and delusional psychopathology with this 'hierarchical approach' to nosology. When both kinds of symptoms were present in one case, and the patient seemed schizophrenic *and* obsessive-compulsive, then the hierarchically superior diagnosis of schizophrenia was made and the other diagnosis, OCD, was not."

https://doi.org/10.1017/S1092852900005575 Published online by Cambridge University Press

relationships between the two disorders were always apparent. This can be seen from an historical perspective: The very term "obsession" originated in relationship to its kindred term, "possession." Both words stemmed from the theological atmosphere of the Inquisition and the belief that devils either "possessed" someone, who then deserved to be killed, or merely "obsessed" them, in which case the victim resisted possession, and therefore could still be saved. The critical distinction between these two states was "resistance," always present in obsessions and always absent in possession. Obsessed victims resisted the devil, possessed victims did not. The two states were never easy to tell apart, as the anguished transcripts of the inquisition demonstrate again and again in abundant detail.[3] Nowadays, of course, we replace the term "possession" with "delusion" but continue to be vexed by difficulties when we try to separate the two categories.[2]

"Once we try to abandon the hierarchical principal, we are left struggling with incredible numbers of disorders and comorbidities. To our dismay, we wind up listing four, five, or even more mental disorders in one patient, while we know in our hearts that we are violating the phenomenological reality of their suffering and of the conditions that we are investigating."

One of our more recent "parents," Jaspers, perhaps the principal architect of the "older nosological schemes," tried to get around the enmeshment of obsessional and delusional psychopathology with this "hierarchical approach" to nosology.[4] When both kinds of symptoms were present in one case, and the patient seemed schizophrenic *and* obsessive compulsive, then the hierarchically superior diagnosis of schizophrenia was made and the other diagnosis, obsessive-compulsive disorder (OCD), was not. But this did *not* mean that schizophrenia and obsessive-compulsive disorder as mutually exclusive disorders, completely separate and unrelated, with no coexistence between them. Jaspers realized that persons with schizophrenia are often anxious, depressed and obsessive-compulsive; persons with manic-depression are often anxious, etc. He was trying to find order in a field with boundaries that often seem as fixed as they are in a custard pie. Of course, the modern *Diagnostic and Statistical Manual of Mental Disorders*, fourth editon, approach does break with Jasper's hierarchical nosological schema by instead endorsing the principal of comorbidity. Nowadays, there is no longer a hierarchy, so all disorders are routinely enumerated (of course, this is only sometimes true—when schizophrenics are anxious or dysthymic, we still ignore these diagnoses!). However, this modern approach has not "contradicted exclusivity and introduced much uncertainty and confusion that the heretofore neat and orderly picture of schizophrenia and OCD as separate entities." [1] It just gives us a different way to deal with the uncertainty and confusion that was always present and acknowledged.

Are we better off with the comorbidity of present-day approaches? I, for one, am not so certain. In the first place, there is the inconsistency mentioned above. We still have hierarchies, although they are more covert— comorbid schizophrenia and anxiety or dysthymia is diagnosed as one disorder while comorbid schizophrenia and OCD are diagnosed, rather inconsistently, I think, as two. Secondly, such hierarchies are often reasonable. A "custard pie" with raisins in it is not a "custard pie" *and* a "raisin pie." Once we try to abandon the hierarchical principal, we are left struggling with incredible numbers of disorders and comorbidities. To our dismay, we wind up listing four, five, or even more mental disorders in one patient, while we know in our hearts that we are violating the phenomenological reality of their suffering and of the conditions that we are investigating. Furthermore, more specific to schizophrenia and OCD, the present-day emphasis on comorbidity obscures at least one possible alternative way of formulating the relationship between schizophrenia and OCD beyond McGloshan's "three alternate hypotheses."[1] The fourth hypothesis: Obsessive-compulsive psychopathology seen in schizophrenia is qualitatively different from obsessive-compulsive psychopathology seen in OCD. For example, obsessions and compulsions seen in schizophrenia might sometimes lack the criteria of "resistance" and in these instances be fundamentally different from the apparently similar but in fact resisted obsessions and compulsions typically seen in OCD.

This fourth hypothesis could be empirically tested. It may turn out to be useful, as McGlashan seems to prefer, to redefine obsessions and compulsions as "repetitive mental content," thereby tossing out the classical emphasis on "resistance."[1] On the other hand, such an approach may turn out to be shortsighted, in which case the old nosologists were not so far off after all! CNS

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https://doi.org/10.1017/S1092852900005575 Published online by Cambridge University Press

NEURONTIN®
(Gabapentin Capsules)

Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE

Neurontin® (gabapentin) is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy.

CONTRAINDICATIONS

Neurontin® is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Withdrawal Precipitated Seizure, Status Epilepticus

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

In the placebo-controlled studies, the incidence of status epilepticus in patients receiving Neurontin® was 0.6% (3 of 543) versus 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients treated with Neurontin® across all studies (controlled and uncontrolled) 31 (1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with Neurontin® is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with Neurontin®.

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. (See PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility.) The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies comprising 2085 patient-years of exposure, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of Neurontin®. Without knowledge of the background incidence and recurrence in a similar population not treated with Neurontin®, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

Sudden and Unexplained Deaths

During the course of premarketing development of Neurontin®, 8 sudden and unexplained deaths were recorded among a cohort of 2203 patients treated (2103 patient-years of exposure). Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving Neurontin® (ranging from 0.0005 for the general population of epileptics, to 0.003 for a clinical trial population similar to that in the Neurontin® program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the Neurontin® cohort and the accuracy of the estimates provided.

PRECAUTIONS

Information for Patients

Patients should be instructed to take Neurontin® only as prescribed.

Patients should be advised that Neurontin® may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on Neurontin® to gauge whether or not it affects their mental and/or motor performance adversely.

Laboratory Tests

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Neurontin®. The value of monitoring Neurontin® blood concentrations has not been established. Neurontin® may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs.

Drug Interactions

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs.

The drug interaction data described in this section were obtained from studies involving healthy adults and patients with epilepsy.

Phenytoin: In a single and multiple dose study of Neurontin® (400 mg T.I.D.) in epileptic patients (N = 8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

Carbamazepine: Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg T.I.D.; N = 12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

Valproic Acid: The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg T.I.D.; N = 17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

Phenobarbital: Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg T.I.D.; N = 12) are identical whether the drugs are administered alone or together.

Cimetidine: In the presence of cimetidine at 300 mg Q.I.D. (N = 12) the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive: Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg T.I.D.; N = 13). The Cmax of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox®): Maalox reduced the bioavailability of gabapentin (N = 16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox. It is recommended that gabapentin be taken at least 2 hours following Maalox administration.

Effect of Probenecid: Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

Drug/Laboratory Tests Interactions

Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma concentrations in humans receiving 3600 mg per day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. Studies to attempt to define a mechanism by which this relatively rare tumor type is occurring are in progress. The relevance of this finding to carcinogenic risk in humans is unclear.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and two *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on an mg/m² basis).

Pregnancy

Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m² basis. The no-effect level was 500 mg/kg/day or approximately ½ of the human dose on a mg/m² basis.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m² basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m² basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m² basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m² basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately ¼ to 8 times the maximum human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers

It is not known if gabapentin is excreted in human milk and the effect on the nursing infant is unknown. However, because many drugs are excreted in human milk, Neurontin® should be used in women who are nursing only if the benefits clearly outweigh the risks.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Geriatric Use

No systematic studies in geriatric patients have been conducted. Adverse clinical events reported among 59 Neurontin® exposed patients over age 65 did not differ in kind from those reported for younger individuals. The small number of older individuals evaluated, however, limits the strength of any conclusions reached about the influence, if any, of age on the kind and incidence of adverse events or laboratory abnormality associated with the use of Neurontin®.

Because Neurontin® is eliminated primarily by renal excretion, the dose of Neurontin® should be adjusted as noted in DOSAGE AND ADMINISTRATION (Table 2) for elderly patients with compromised renal function. Creatinine clearance is difficult to measure in outpatients and serum creatinine may be reduced in the elderly because of decreased muscle mass. Creatinine clearance (C_{Cr}) can be reasonably well estimated using the equation of Cockcroft and Gault:

for females $C_{Cr} = (0.85)(140\text{-age})(wt)/[(72)(S_{Cr})]$

for males $C_{Cr} = (140\text{-age})(wt)/[(72)(S_{Cr})]$

where age is in years, wt is in kilograms and S_{Cr} is serum creatinine in mg/dL.

ADVERSE REACTIONS

The most commonly observed adverse events associated with the use of Neurontin® in combination with other antiepileptic drugs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus.

Approximately 7% of the 2074 individuals who received Neurontin® in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%).

Incidence in Controlled Clinical Trials

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 1% of Neurontin®-treated patients with epilepsy participating in placebo-controlled trials and were numerically more common in the Neurontin® group. In these studies, either Neurontin® or placebo was added to the patient's current antiepileptic drug therapy. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when Neurontin® was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

TABLE 1. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials (Events in at least 1% of Neurontin® (Gabapentin Capsules) patients and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Neurontin®[a] N = 543 %	Placebo[a] N = 378 %	Body System/ Adverse Event	Neurontin®[a] N = 543 %	Placebo[a] N = 378 %
Body As A Whole			Nervous System (continued)		
Fatigue	11.0	5.0	Tremor	6.8	3.2
Weight Increase	2.9	1.6	Nervousness	2.4	1.9
Back Pain	1.8	0.5	Dysarthria	2.4	0.5
Peripheral Edema	1.7	0.5	Amnesia	2.2	0.0
			Depression	1.8	1.1
Cardiovascular			Thinking Abnormal	1.7	1.3
Vasodilatation	1.1	0.3			
			Twitching	1.3	0.5
Digestive System			Coordination Abnormal	1.1	0.3
Dyspepsia	2.2	0.5			
Mouth or Throat Dry	1.7	0.5	Respiratory System		
Constipation	1.5	0.8	Rhinitis	4.1	3.7
Dental Abnormalities	1.5	0.3	Pharyngitis	2.8	1.6
Increased Appetite	1.1	0.8	Coughing	1.8	1.3
Hematologic and Lymphatic Systems			Skin and Appendages		
Leukopenia	1.1	0.5	Abrasion	1.3	0.0
			Pruritus	1.3	0.5
Musculoskeletal System					
Myalgia	2.0	1.9	Urogenital System		
Fracture	1.1	0.8	Impotence	1.5	1.1
Nervous System			Special Senses		
Somnolence	19.3	8.7	Diplopia	5.9	1.9
Dizziness	17.1	6.9	Amblyopia[b]	4.2	1.1
Ataxia	12.5	5.6	Laboratory Deviations		
Nystagmus	8.3	4.0	WBC Decreased	1.1	0.5

[a] Plus background antiepileptic drug therapy

[b] Amblyopia was often described as blurred vision.

Other events in more than 1% of patients but equally or more frequent in the placebo group included: headache, viral infection, fever, nausea and/or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne.

Among the treatment-emergent adverse events occurring at an incidence of at least 10% of Neurontin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with Neurontin®. The incidence of adverse events increased slightly with increasing age in patients treated with either Neurontin® or placebo. Because only 5% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse events by race.

Other Adverse Events Observed During All Clinical Trials

Neurontin® has been administered to 2074 individuals during all clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 individuals exposed to Neurontin® who experienced an event of the type cited on at least one occasion while receiving Neurontin®. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body As A Whole: *Frequent:* asthenia, malaise, face edema; *Infrequent:* allergy, generalized edema, weight decrease, chill; *Rare:* strange feelings, lassitude, alcohol intolerance, hangover effect.

Cardiovascular System: *Frequent:* hypertension; *Infrequent:* hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur; *Rare:* atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis.

Digestive System: *Frequent:* anorexia, flatulence, gingivitis; *Infrequent:* glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly; *Rare:* dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perleche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm.

Endocrine System: *Rare:* hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance.

Hematologic and Lymphatic System: *Frequent:* purpura most often described as bruises resulting from physical trauma; *Infrequent:* anemia, thrombocytopenia, lymphadenopathy; *Rare:* WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased.

Musculoskeletal System: *Frequent:* arthralgia; *Infrequent:* tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test; *Rare:* costochondritis, osteoporosis, bursitis, contracture.

Nervous System: *Frequent:* vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility; *Infrequent:* CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis; *Rare:* choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, aphasia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: *Frequent:* pneumonia; *Infrequent:* epistaxis, dyspnea, apnea, *Rare:* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatological: *Infrequent:* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare:* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: *Infrequent:* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; *Rare:* kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain.

Special Senses: *Frequent:* abnormal vision; *Infrequent:* cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness; *Rare:* eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell.

Postintroduction Reports

Adverse events associated with Neurontin® that have been received since market introduction, that are not listed above, and that may have no causal relationship to drug, include the following: erythema multiforme, Stevens-Johnson syndrome and elevated liver function tests.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of Neurontin® has not been evaluated in human studies.

OVERDOSAGE

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

Acute oral overdoses of Neurontin® up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

Neurontin® is recommended for add-on therapy in patients over 12 years of age. Evidence bearing on its safety and effectiveness in pediatric patients below the age of 12 is not available.

Neurontin® is given orally with or without food.

The effective dose of Neurontin® is 900 to 1800 mg/day and given in divided doses (three times a day) using 300- or 400-mg capsules. Titration to an effective dose can take place rapidly, over a few days, giving 300 mg on Day 1, 300 mg twice a day on Day 2, and 300 mg three times a day on Day 3. To minimize potential side effects, especially somnolence, dizziness, fatigue, and ataxia, the first dose on Day 1 may be administered at bedtime. If necessary, the dose may be increased using 300- or 400-mg capsules three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the T.I.D. schedule should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize Neurontin® therapy. Further, because there are no significant pharmacokinetic interactions among Neurontin® and other commonly used antiepileptic drugs, the addition of Neurontin® does not alter the plasma levels of these drugs appreciably.

If Neurontin® is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended as follows:

TABLE 2. Neurontin® Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose (mg/day)	Dose Regimen (mg)
>60	1200	400 T.I.D.
30–60	600	300 B.I.D.
15–30	300	300 Q.D.
<15	150	300 Q.O.D.[c]
Hemodialysis	—	200-300[b]

[c] Every other day

[b] Loading dose of 300 to 400 mg in patients who have never received Neurontin®, then 200 to 300 mg Neurontin® following each 4 hours of hemodialysis

Caution: Federal law prohibits dispensing without prescription.

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Revised January 1997
PD-116-JA-0639-AT(027)
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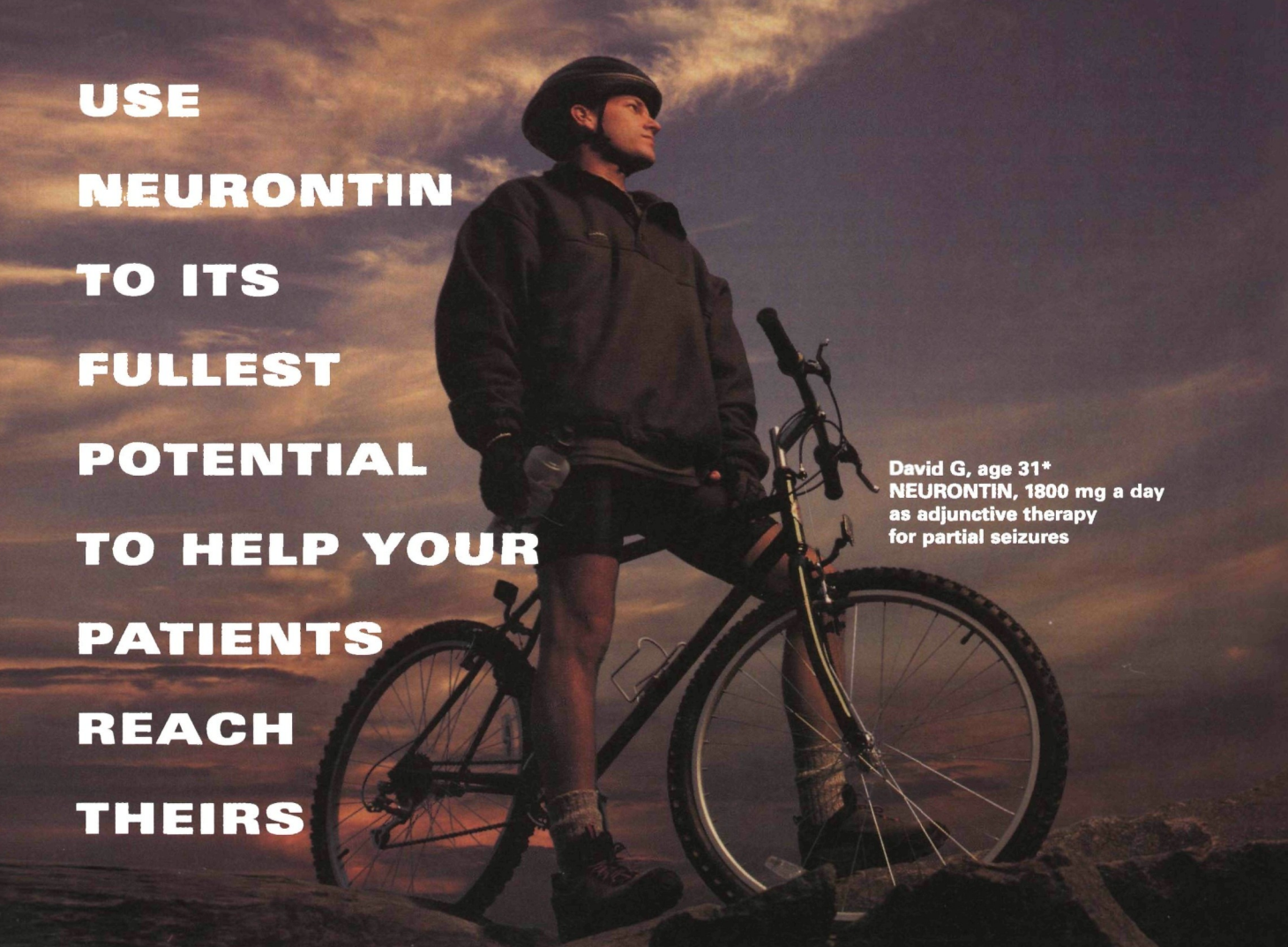

NEURONTIN ADJUNCTIVE THERAPY OFFERS EASY AND RAPID TITRATION FOR IMPROVED INDIVIDUAL CONTROL

- NEURONTIN can be rapidly titrated to effect, up to 1800 mg/day (600 mg tid).†‡§ In clinical studies, doses of 3600 mg/day were well tolerated in a small number of patients during short-term administration
- NEURONTIN has no pharmacokinetic interactions with commonly prescribed first-line AEDs: valproic acid, carbamazepine, phenobarbital, or phenytoin
- NEURONTIN offers the confidence that comes from experience in over 300,000 patients

*Hypothetical patient

Please see adjacent page for a brief summary of full prescribing information.

NEURONTIN®
gabapentin capsules
100 mg, 300 mg, 400 mg

WELL TOLERATED...EASILY TITRATED...PROVEN EFFICACY

NEURONTIN is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults (>12 years old).

NEURONTIN is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

In placebo-controlled studies, status epilepticus occurred in 0.6% (3/543) of NEURONTIN-treated patients vs 0.5% (2/378) of placebo-treated patients. Because adequate historical data are not available, it is impossible to say whether treatment with NEURONTIN is associated with a higher or lower rate of status epilepticus.

In placebo-controlled studies (n=543), the most common adverse events associated with NEURONTIN were somnolence (19.3% vs 8.7% with placebo); dizziness (17.1% vs 6.9% with placebo); ataxia (12.5% vs 5.6% with placebo); fatigue (11% vs 5% with placebo); nystagmus (8.3% vs 4% with placebo).

† Because NEURONTIN is eliminated renally, dosage adjustment is recommended in renally compromised patients or those patients undergoing hemodialysis. Please see Dosage and Administration section of full prescribing information for schedule.

‡ *To minimize potential side effects, especially somnolence, dizziness, fatigue, and ataxia, the first dose on Day 1 may be administered at bedtime.*

§ Titration to an effective dose can take place rapidly, over a few days, giving 300 mg on Day 1, 300 mg twice a day on Day 2, and 300 mg three times a day on Day 3. Once titrated to 900 mg/day (300 mg tid), if necessary the dose may be increased using 300-mg or 400-mg capsules three times a day, up to 1800 mg/day.

https://doi.org/10.1017/S1092852900005575 Published online by Cambridge University Press