双極性障害に対する有効な維持療法

長時間作用型リスペリドンは双極I型障害患者の再発までの時間を遅らせる

Maintenance therapy with long-acting risperidone delays time to relapse in patients with bipolar I disorder

2009年American Psychiatric Association学会で発表された新たなデータから、長時間作用型リスペリドンは双極I型障害患者の再発までの時間を有意に遅延させることが示された。無作為化二重盲検プラセボコントロール長期スタディが行われ、薬物療法で落ち着いているかまたは急性躁病エピソードか混合性エピソード発現中の双極I型障害のDSM-IVクライテリアに合致する患者における維持療法としてのリスペリドンの効果が評価された。スタディの第一段階で303人の患者がオープンラベルの長時間作用型リスペリドン26週間投与にて安定した。二重盲検の段階で患者は長時間作用型リスペリドンによる維持療法群（154人）またはプラセボ群（149人）に無作為に割り付けられた。治療期間中央値はリスペリドン群で9ヵ月であり、プラセボ群で5ヵ月であった。一次エンドポイントは何らかの気分エピソード（うつ病、躁病、または混合性）再発までの時間であった。再発までの時間はプラセボ群と比較しリスペリドン群で有意に長かった（p<0.001）。さらに、二重盲検段階の再発率はリスペリドン群（30%；42/140）でプラセボ群（56%；76/135）よりも低かった。リスペリドン投与量の中央値は25mgであった。

Full Text

New data presented at the 2009 American Psychiatric Association annual meeting demonstrates that maintenance therapy with long-acting risperidone significantly delays time to relapse in patients with bipolar I disorder.

Bipolar Disorder is often characterized by debilitating mood swings from extreme highs (mania) to extreme lows (depression). Type I Bipolar Disorder is characterized based on the occurrence of at least one manic episode, with or without the occurrence of a major depressive episode.

A randomized, double-blind, placebo-controlled, long-term study was conducted to evaluate the effect of long-acting risperidone as maintenance therapy in patients who met DSM-IV criteria for Bipolar I Disorder who were stable on medications or experiencing an acute manic or mixed episode. In the first phase of the study, 303 patients were stabilized on open-label risperidone for 26 weeks. In the double-blind phase, patients were randomized to either maintenance therapy with risperidone (N=154) or placebo (N=149). The median duration of treatment was nine months for patients in the risperidone group and five months for patients in the placebo group. The primary endpoint was time to relapse of any mood episode (depression, mania, or mixed).

Time to relapse was significantly longer in patients receiving risperidone monotherapy as compared to placebo (p<0.001). In addition, the rate of relapse during the double-blind treatment phase was lower among patients in the risperidone group (30 percent; 42/140) compared with the placebo group (56 percent; 76/135). The median dose of risperidone was 25 mg.

The most common adverse reactions in clinical trials in patients with bipolar disorder were weight increase (5% in monotherapy trial) and tremor and parkinsonism (greater than or equal to 10% in adjunctive therapy).

"This is the first randomized controlled study to demonstrate the efficacy of RLAT as a maintenance therapy in patients with Bipolar Disorder," said Joseph Palumbo, M.D., Franchise Medical Leader, Psychiatry, Central Nervous System and Pain Therapeutic Area, Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD). "These findings are important because the clinical course of Bipolar Disorder is often unpredictable and relapses can be very debilitating."

The study was presented and sponsored by Janssen, a Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc and J&JPRD.

APA2009特集

新たな統合失調症治療薬

Phase 3トライアルの結果、lurasidoneは統合失調症治療において有効であり忍容性も良好であることが示された

Phase 3 trial finds lurasidone to be effective and well tolerated for treatment of schizophrenia

急性期の統合失調症治療に対するlurasidoneの初めてのphase 3トライアルの結果、この薬剤がプラセボよりも有意に有効であり忍容性も良好で脱落率も比較的低いことが報告された、と第162回American Psychiatric Association学会で発表された。無作為化プラセボコントロール二重盲検多国籍トライアルPEARL 1 ：Program to Evaluate the Antipsychotic Response to Lurasidone（Lurasidoneの抗精神病作用を評価するプログラム）において急性期の統合失調症患者に一日40mg、80mg、120mgのいずれかの用量のlurasidoneを6週間投与しプラセボと比較し評価した。一日80mgのlurasidone投与により、Positive and Negative Syndrome Scale（PANSS）総スコア（一次エンドポイント）およびClinical Global Impressions Severity scale（CGI-S、重要な二次エンドポイント）が第2週から第6週までの全ての受診時において改善していた。lurasidoneの体重への影響はプラセボと同等であり（体重変化中央値はlurasidone群全体で0.3kgに対しプラセボ群で0kg）、脂質および血糖値に対する影響も同等であった。またlurasidone群全体の脱落率はプラセボと比較し低く（31%対43%）忍容性が良好であり、有害事象による脱落率も低かった（lurasidone群全体とプラセボ群とでそれぞれ6%と2%）。

Full Text

The first phase 3 trial of lurasidone for treatment of acute schizophrenia reports the drug is significantly better than placebo, was well tolerated and has a relatively low discontinuation rate according to findings presented at the 162nd Annual Meeting of the American Psychiatric Association.

PEARL 1 (Program to Evaluate the Antipsychotic Response to Lurasidone) is part of an extensive worldwide phase 3 clinical development program, involving more than 2,000 patients, intended to evaluate the safety and efficacy of lurasidone for the treatment of schizophrenia. In addition to the primary finding of this six-week, double-blind, placebo-controlled trial that lurasidone 80 mg/day was significantly more effective than placebo at the study endpoint, lurasidone was associated with greater improvement on both the Positive and Negative Syndrome Scale (PANSS) total score (primary endpoint) and the Clinical Global Impressions Severity scale (CGI-S, key secondary endpoint) at all visits between weeks two and six. PEARL 1 also evaluated two other fixed doses of lurasidone, 40 mg/day and 120 mg/day, which did not demonstrate separation from placebo on the PANSS or CGI-S at study endpoint.

"People with schizophrenia need new treatment options that offer a combination of efficacy, safety and tolerability so that the symptoms can be stabilized and effectively treated," said Henry Nasrallah, M.D., professor of psychiatry and neuroscience and director of the schizophrenia research program at the University of Cincinnati College of Medicine. "Lurasidone has the potential to be an important new therapeutic option for patients with schizophrenia."

Lurasidone's effect on weight was similar to placebo (median change 0.3 kg for overall lurasidone group vs. 0 kg for placebo) as was its effect on lipid and glucose measures. Lurasidone was also well tolerated with a lower overall discontinuation rate (31%) compared to placebo (43%) and few adverse event-related discontinuations (6% and 2% for the overall lurasidone group and placebo, respectively).

Adverse events seen in the trial were generally mild. The most commonly reported adverse events for lurasidone (greater than 5% and at least twice the rate of placebo) were akathisia (17.6% vs. 3.1% placebo), somnolence (11.7% vs. 5.5%), parkinsonism (6.8% vs. 0), and increased weight (5.1% vs. 2.4%).

"The development program for lurasidone is intended to establish efficacy for the core symptoms of schizophrenia, characterize its safety profile and explore its effects in the treatment of cognitive impairment and other areas not adequately addressed by current therapies," said Antony Loebel, M.D., vice president of clinical research, Dainippon Sumitomo Pharma America, Inc. "As a large, global trial, the PEARL 1 study is an important new addition to the existing clinical trial database."

This randomized, placebo-controlled, double-blind, multinational clinical trial evaluated the efficacy and safety of lurasidone 40 mg, 80 mg and 120 mg once daily compared to placebo, over six weeks in patients with acute schizophrenia. Patients were diagnosed with schizophrenia (using DSM-IV criteria) and were required to have an acute exacerbation of psychotic symptoms with a PANSS total score of 80 or higher at study baseline.

A total of 500 patients were randomized equally to the four treatment arms. The pre-specified primary endpoint was change from baseline in the PANSS total score over the six-week study duration for each lurasidone dose group vs. placebo. A key secondary endpoint was the change from baseline in CGI-S over the six-week study period. Efficacy data were statistically analyzed using a mixed model for repeated measures. Multiple safety assessments were done, including vital signs, weight, ECGs, movement disorder scales (SAS, BAS, AIMS), and laboratory assessments.

The study was conducted at 51 sites worldwide. Twenty-two sites in the United States randomized 278 patients, 21 sites in Europe randomized 148 patients and eight sites in Asia randomized 48 patients. The majority of trial participants were male with a mean age of 39 years. The mean time since initial diagnosis was approximately 14 years, and patients had, on average, four or more hospitalizations prior to study entry.

Lurasidone has been studied in three double-blind, placebo-controlled, six-week trials involving more than 650 patients with schizophrenia, of which 392 patients received lurasidone. Two of the three studies demonstrated that lurasidone had superior efficacy compared to placebo at doses ranging between 40 mg and 120 mg/day. A third study, which examined three fixed doses of lurasidone (20 mg, 40 mg, and 80 mg/day) did not show statistical differences vs. placebo. This trial is regarded as "failed," or inconclusive, as haloperidol (10 mg/day), which was included for purposes of assay sensitivity, also failed to distinguish from placebo.

治療によりうつ病患者の認知機能が改善する

経頭蓋磁気刺激（TMS）療法は大うつ病患者の認知機能を改善する

Transcranial magnetic stimulation (TMS) therapy improves cognitive function in patients with major depressive disorder

経頭蓋磁気刺激（TMS）療法は大うつ病患者の総合的な認知機能および短期の言葉の記憶を改善したと第162回American Psychiatric Association学会で発表された。認知機能は薬物治療に抵抗性の大うつ病患者におけるNeuroStar TMS療法の多施設無作為化コントロールトライアルにおいて評価した（有効なTMS群155人、シャムTMS群146人）。全体的な認知機能、短期および長期の記憶に関する特異的な計測（それぞれMini Mental Status Examination、Buschke Selective Reminding Test、Autobiographical Memory Interview-Short Form）を初回治療前、TMSを毎日施行する集中治療コース期間中の4および6週の時点で行った。6週終了後に各治療群の臨床経過で分類した。TMS群のみにおいては、TMSが有効であった者において無効であった者と比較し、Buschke Selective Reminding Testにおける短期記憶（4週目P=0.0116；6週目P=0.0038）および長期記憶（4週目P=0.0463；6週目P=0.0012）が統計学的に有意に改善した。この認知機能改善はプラセボ投与患者では認められなかった。

Full Text

Transcranial magnetic stimulation (TMS) therapy improved both overall cognitive function and short-term verbal memory in patients with major depressive disorder according to research presented at the 162nd Annual Meeting of the American Psychiatric Association.

Diminished ability to think, concentrate, and make decisions is a core symptom of depression. This is often further worsened by some common depression treatments, such as some classes of medications. Most notably, electroconvulsive therapy (ECT), while extremely effective, has high rates of cognitive impairment and long-term or even permanent memory loss.

"In this study, NeuroStar TMS Therapy demonstrated no negative effect on cognition, and evidence suggests that it may even improve certain cognitive functions in depressed patients," said psychiatrist Phil Janicak, M.D., Professor of Psychiatry at Rush University-Chicago and a principal investigator of the trial. "Many patients, by virtue of their depression, already have diminished cognitive functioning. Receiving an effective treatment like TMS, which appears to have no adverse cognitive effects, may benefit millions of people who require alternate treatment options," Janicak added.

Cognitive function was examined in a multi-site, randomized controlled trial of NeuroStar TMS Therapy in patients with pharmacoresistant major depressive disorder (N=155 active TMS, N=146 sham TMS). Specific measures of global cognition (Mini Mental Status Examination), short-term (Buschke Selective Reminding Test) and long-term memory (Autobiographical Memory Interview-Short Form) were obtained prior to first treatment, and at four and six weeks during an acute treatment course of daily TMS. The results showed no significant difference between active TMS and placebo TMS treatment conditions on any of these measures of cognitive function, which indicates that NeuroStar TMS Therapy had no negative effect on cognition.

Additionally, each treatment group was stratified by clinical outcome (HAMD24 responder) at the end of six weeks. Within the TMS group only, there was a statistically significant improvement on the Buschke Selective Reminding Test in the TMS responders compared to TMS non-responders for both short-term recall (P = 0.0116 at four weeks; P = 0.0038 at six weeks) and delayed recall (P = 0.0463 at four weeks; P = 0.0012 at six weeks). This improvement in cognitive function was not seen in placebo-treated patients.

"We believe that the reason for the lack of negative cognitive effects with NeuroStar TMS Therapy is likely due to the focused stimulation of a key brain region, rather than the whole brain effects of both medications and ECT," said Mark A. Demitrack, M.D., Chief Medical Officer for Neuronetics Inc., a psychiatrist, and the study's lead author. "The fact that NeuroStar caused no negative effects on cognition, and appeared to improve some measures of cognition in some patients, is a testament to the safety of this new non-systemic and non-invasive treatment option."

APA2009特集

ADHD症状の改善

Guanfacineは反抗的な症状のあるADHD患者の症状を有意に改善する

Guanfacine shows significant ADHD symptom improvement in patients with oppositional symptoms

用量変更可能な無作為化プラセボコントロールスタディにおいて選択的α2A作動薬guanfacine徐放製剤は、ADHD評価スケールIVを用いた計測で反抗的症状を有すると診断された6～12歳のADHD小児のADHD症状を有意に改善することが示された。このデータは第162回American Psychiatric Association学会で発表された。Guanfacineはまた、三つの異なる評価スケール（Clinical Global Impressions-Improvement [CGI-I]、Conduct Problem Subscale of the New York Parent Rating Scale-School-Aged [NYPRS-S]、および Parent Stress Index-Short Form [PSI/SF]アンケート）で計測した症状も改善した。CGI-Iスケールにおいては10人中7人においてプラセボと比較し”非常によく改善”または”よく改善”と評価された（71.5%対32.0%；P<0.001）。Conduct Problem Subscale of the NYPRS-Sにおいてもguanfacine群においてプラセボ群と比較し有意な症状の軽減が認められた(-16.0対-9.6；P<0.001）。PSI/SFスケールにおいては、guanfacine群は17.0点減少したのに対しプラセボ群では7.7点の減少であった（P=0.002）。重篤な有害事象は認められなかった。

Full Text

In a randomized, placebo-controlled, flexible-dose study, guanfacine extended release, a selective alpha-2A-agonist, demonstrated significant ADHD symptom improvement in children aged 6 to 12 years with a diagnosis of ADHD and the presence of oppositional symptoms as measured by the ADHD Rating Scale-IV. The data was presented at the American Psychiatric Association's 162nd annual meeting.

"A significant number of pediatric ADHD patients present with behaviors such as anger, resentfulness, defiance, and arguing with adults. It can be complicated for physicians and caregivers to find the right medication to control symptoms for children with ADHD exhibiting these behaviors," said Daniel Connor, M.D., professor and division chief of child and adolescent psychiatry at the University of Connecticut Medical School. "When considered with the primary efficacy results of the current study, these data provide additional support for the clinical efficacy of guanfacine for treating ADHD in this patient population."

In this randomized, placebo-controlled, flexible-dose study, guanfacine demonstrated significant ADHD symptom improvement in patients with oppositional symptoms as measured by the ADHD Rating Scale-IV (ADHD-RS-IV), a scale frequently used in ADHD clinical trials. In results from this study, guanfacine also demonstrated symptom improvement as measured by three different rating scales: the Clinical Global Impressions-Improvement (CGI-I), the Conduct Problem Subscale of the New York Parent Rating Scale-School-Aged (NYPRS-S), and the Parent Stress Index-Short Form (PSI/SF) questionnaire.

When using the CGI-I scale, investigators rated 7 out of 10 patients as "very much improved" or "much improved" compared with placebo (71.5 percent vs 32.0 percent; P<0.001). The CGI-I scale is a standard assessment used to rate the severity of a patient's illness and improvement over the course of the study.

Significantly greater symptom reductions were also seen on the Conduct Problem Subscale of the NYPRS-S in the guanfacine group compared to placebo (-16.0 vs -9.6; P<0.001). In this parent-rated scale, numerous symptoms including anger, defiance, arguing with adults, and loss of temper were assessed in children on a four-point scale and a higher score indicated greater problems. Additional improvement was demonstrated on the PSI/SF, a parent rated 36-item questionnaire that measured stressful areas in parent-child interactions. On the PSI/SF scale, the guanfacine group reduced its score by 17.0 compared to 7.7 for the placebo group (P=0.002).

In this study, the most commonly reported treatment emergent adverse events (greater than or equal to 10 percent) were somnolence, headache, sedation, upper abdominal pain, fatigue and irritability. The majority of treatment emergent adverse events were mild to moderate in severity. There were no serious adverse events.

学校でのADHD症状は親にとって心配の種である

ヨーロッパ介護者調査では子供および家庭におけるADHDの影響に焦点を当てている

European Caregiver Survey highlights the impact of ADHD on the child and the family

注意欠損多動性障害（ADHD）の子供の両親は、両親とのプライベートな時間における子供のADHD行動の影響と同様、学校でのADHD症状にも重大な関心を示しているとのヨーロッパ介護者調査の結果が第162回American Psychiatric Association学会で発表された。この調査において、ドイツ、イタリア、スペインおよび英国の50%近くの親が、彼らの子供が評価を必要とするADHD症状を有しているかを決断するのに彼らが重要な役割を果たしていると回答した。また彼らは家庭でのADHD症状よりも学校でのADHD症状について最も懸念しており（それぞれ17%と67%）、学校のある日は通常内服させていた。さらに、調査の結果ほとんどの親が専門医を少なくとも年2回受診しており、親のADHDの知識は診断時に与えられたサポートとじかに関連していた。しかし、彼らのうち専門医から供給された知識的なサポート（ADHDの子供をもつ家庭への書面での情報、地域または国のサポートグループに関する情報、ADHDを有する子供に対する書面での情報、およびオンラインの情報）により”よく情報を提供された”と感じた者はわずか半分（51%）であった。

Full Text

Parents of children with Attention Deficit Hyperactivity Disorder (ADHD) express key concerns about their child's ADHD symptoms at school as well as the impact of the ADHD behavior on the parents' personal time according to results from the European Caregiver Survey presented at the American Psychiatric Association's 162nd annual meeting.

The survey also revealed key findings surrounding parents' role in assessment and treatment for their child. Additionally, the survey suggested that informational needs may not be met adequately for these children with ADHD and their families. Conducted in partnership with ADHD advocacy groups in four EU countries, the survey analyzed parental impressions surrounding the impact of ADHD on their child, themselves and their family, as well as their child's ADHD treatment plan.

In the survey, nearly 50 percent of parents across Germany, Italy, Spain and the UK indicated that they played a key role in determining whether their child had ADHD symptoms requiring assessment. Parents also reported being most concerned about their child's ADHD symptoms at school (67 percent), compared with ADHD symptoms at home (17 percent), and that medication was usually taken on school days. Further, the survey showed that most parents see a specialist at least twice a year, and that parents' level of knowledge about ADHD is directly linked to the support provided at the time of diagnosis. However, only half (51 percent) of these respondents felt "well informed" by the informational support provided by the specialist, which included written information for families of children with ADHD, information on local or national support groups, written information for the child with ADHD, and online information.

"ADHD is a commonly diagnosed psychiatric disorder in children and adolescents. In fact, ADHD affects an estimated 5.3 percent of children and adolescents 18 years of age or younger worldwide, with large variability between countries," said Dr. Myriam Menter, president of ADHD-Europe. "Keeping this in mind, it is important that physicians know how ADHD is currently being perceived by parents of children with the disorder and that they fully understand parents' concerns about managing their child's symptoms. With the help of this survey, physicians can better devise management and support solutions for patients with ADHD and their families."

Outside of school, the majority of parents across Europe reported that the impact of ADHD on their personal and family time is a key factor with the disorder. The impact was noted across a number of activities, but in particular ADHD was felt to impact personal time for themselves and time with their partner or with the family.

When asked about ADHD management, most parents (80 percent) felt involved in the decision for their child, and most received their preferred management option. Although parents experienced mixed emotions with having to put their child on medication, the survey showed that many parents became more positive toward the idea of medication because it made a positive improvement in their child's symptoms.

The European Caregiver survey was developed by Shire and conducted in conjunction with ADHD advocacy groups in Germany, Italy, Spain and the UK. Following are differing perceptions on ADHD and its impact on family life seen between these countries:

・Impact at school - The majority of parents across all surveyed markets reported their child's ADHD symptoms to be most concerning when at school, compared to at home or when engaging in social activities. Parents in Italy were most concerned about their child's ADHD symptoms at school (85 percent), followed by parents in Spain (77 percent), Germany (60 percent), and the UK (57 percent).

・ Impact on personal time - Whilst parents in all European countries consistently reported the impact on personal time as their greatest factor with their child's ADHD, over three-quarters of Italian parents (77 percent) reported that their personal time is most impacted compared with just over half of Spanish parents (52 percent).

・Time to diagnosis - In the UK, 65 percent of ADHD diagnoses are made within the first two consultations with the doctor or specialist, whereas in other countries the majority of diagnoses occur on the third or subsequent visits.

・Support provided at diagnosis - At diagnosis, only half (51 percent) of European parents reported they were "fairly well informed" or "very well informed" after receiving additional means for support from the physician. Out of the very well informed parents, 79 percent had received written information for families of children with ADHD from the doctor. Parents in the UK believed they were given the most written information, while Italian parents believed they were given the least amount of written information from the specialist.

・Management choice - Most parents in the countries surveyed reported that they felt involved in the management options for their child with ADHD, with the highest involvement seen in Italy (90 percent) and Spain (85 percent), followed by Germany (77 percent) and the UK (74 percent).

This European Caregiver survey was conducted via online interviews of 505 parents and caregivers with at least one child diagnosed with ADHD -- 117 were from Germany, 52 were from Italy, 166 were from Spain, and 170 were from the UK. Respondents were recruited by ADHD advocacy groups in each country either by direct invitation or by means of alerts on intranet sites or in newsletters. The ADHD advocacy groups that participated in the development and execution of this survey include:

・ADHS Deutschland in Germany
・Italian ADHD Family Association (AIFA) in Italy
・ADANA Foundation and Federacion Espanola de Asociaciones de Ayuda al Deficit de Atencion e Hiperactividad (FEAADAH) in Spain
・National Attention Deficit Disorder Information and Support Service (ADDISS), Milton Keynes ADHD (MK ADHD), and Attention Deficit Disorders Uniting Parents (ADDUP) in the UK

This survey was supported by funding from Shire plc.

APA2009特集

児童虐待の心理的影響

児童虐待歴はうつ病入院患者の自殺、薬物乱用、およびパーソナリティ障害に影響する

A history of child abuse impacts rates of suicide, substance abuse, and personality disorder in depressed inpatients

児童虐待歴のあるうつ病入院患者は、自殺企図の増加、薬物使用障害の発症およびパーソナリティ障害の高い発症率などの広範囲の難題に直面する、と2009年American Psychiatric Association学会で発表された。さらに、彼ら犠牲者は精神疾患を早期に発症し精神科的な問題による入院率が高い。児童虐待が自殺のリスクを上昇させることはすでに知られているが、児童虐待の犠牲となったうつ病患者の他の特徴に関する論文は少ない。このスタディの結果は因果関係を確認していないが、公衆衛生の観点から、児童虐待を防ぐもっと積極的なアプローチが重要であることを強調している。さらに大規模なスタディを行い、児童虐待と精神疾患の関連を調査する計画が進行中である。

Full Text

According to a new Mayo Clinic study, a history of child abuse significantly impacts the wide range of challenges facing depressed inpatients. Included are an increase in suicide attempts, prevalence of substance use disorder, and a higher incidence rate of personality disorder. Additionally, these victims also had an earlier onset of mental illness and an increase in psychiatric hospitalizations for psychiatric issues. The study was presented at the American Psychiatric Association 2009 Annual Meeting in San Francisco.

The impact of child abuse already is known to increase the risk of suicide, however the literature about other characteristics of depressed victims of child abuse is scarce. Although the findings of the Mayo study do not confirm causality, the information stresses the importance of more aggressive approaches from the public health perspective to prevent child abuse. "A history of child abuse makes most psychiatric illnesses worse," according to Magdalena Romanowicz, M.D., of the Mayo Clinic and lead author of the study. "We found that it significantly impacts the wide range of characteristics of depressed inpatients including increased risk of suicide attempt, substance abuse, as well as earlier onset of mental illness and more psychiatric hospitalizations. This new information serves as a reminder of the importance of child abuse prevention from a public health perspective."

Dr. Romanowicz says plans are under way to further examine the association between child abuse and metal illness in a larger study of patients.

Other authors of this study include: Gen Shinozaki, M.D.; Victoria Passov, M.D.; Simon Kung, M.D.; Renato Alarcon, M.D.; and David Mrazek, M.D.