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EXHIBIT SCHEDULE

Methylnaltrexone for Opioid-Induced Constipation in Palliative Care

Learning Objectives:

- 1) Describe the mechanism of action of methylnaltrexone.
- 2) Determine the appropriate dose and dosing schedule for methylnaltrexone.
- 3) Identify adverse effects that have been associated with methylnaltrexone.
- 4) Discuss the pivotal studies that methylnaltrexone's approval was based upon.

Introduction

Opioids are the mainstay of pain treatment in patients with malignancies and in many non-cancer patients with moderate-to-severe pain.¹ Despite their effectiveness, usefulness is limited because of numerous adverse effects (AEs), including sedation, respiratory depression, impaired cognition, nausea and vomiting, appetite loss, pruritus, urinary retention, impaired orthostatic tolerance, ileus and constipation.^{2,3} Of these, constipation has been cited by physicians as one of the most important problems associated with the chronic use of opioids.⁴ More than half of all patients receiving palliative care experience opioid-induced constipation.³

Conventional therapies for opioid-induced constipation include laxatives (stool softeners, stimulant, osmotic, lubricant, bulk-forming, osmotic and stimulant) and prokinetic agents.^{1,2} These therapies may have their own set of problems including adverse effects such as diarrhea and cramps, and, furthermore, many patients do not respond to them. Therefore, treatments with a different mechanism of action are needed.² On April 24, 2008, a drug with a novel mechanism of action, methylnaltrexone bromide (Relistor[®], Wyeth/Progenics), hereafter referred to as methylnaltrexone, was approved by the United States Food and Drug Administration (FDA) for the treatment of opioid-induced constipation in patients with advanced illness who have not responded to laxatives.⁵ The drug is administered subcutaneously. Investigational oral and intravenous formulations of methylnaltrexone are also being studied. The manufacturer recently reported that the oral formulation showed "positive activity" in treating opioid-induced constipation in a phase-2 trial in 122 patients with chronic nonmalignant pain, but the intravenous formulation did not meet its primary or secondary endpoints in two phase-3 trials in patients with post-operative ileus.⁶

Pharmacology

Methylnaltrexone is an antagonist of μ (mu) opioid receptors. The binding of opioids to μ -opioid receptors in the central nervous system mediates analgesia. However, the binding of opioids to μ -opioid receptors in the gastrointestinal tract mediates constipation and

other gastrointestinal effects by interfering with gastric motility. A decades-long search to separate the analgesia effects from the gastrointestinal effects has been met with little success.⁷ Opioid receptor antagonists have been investigated for this purpose, but by blocking the effects of opioids in the gastrointestinal tract, they may also block the analgesia effect or cause opioid withdrawal symptoms. Thus, it is necessary to limit the systemic absorption of opioid antagonists or prevent them from crossing the blood-brain barrier and penetrating the central nervous system.⁷ Naloxone, nalmefene and naltrexone are older opioid receptor antagonists, but they easily cross the blood-brain barrier. They are termed tertiary opioid-receptor antagonists because they use three of the structure's available amine bonding sites.⁷

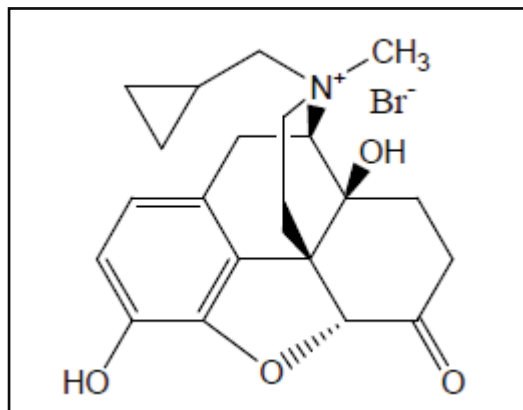
Methylnaltrexone (Figure 1) was created by adding a methyl group to the tertiary opioid-receptor antagonist naltrexone, thereby utilizing all four of the available amine bonding sites.⁷ Thus, it is termed a quaternary μ -opioid-receptor antagonist. The nitrogen is positively charged and therefore the drug cannot cross the blood-brain barrier and only acts in the periphery. Methylnaltrexone shows almost exclusive binding to μ -opioid receptors in the gastrointestinal tract.⁷ Only one other drug in this class, alvimopan, has been approved by the FDA. Alvimopan is available as an oral formulation given twice daily, but it is limited to short-term use (15 doses) in hospitalized patients and is currently indicated for opioid-induced postoperative ileus, not constipation.⁸

Pharmacokinetics

Absorption of subcutaneous methylnaltrexone is rapid, with peak concentrations (C_{max}) occurring approximately 30 minutes following administration.⁹ The volume of distribution at steady state (V_{ss}) is approximately 1.1 L/kg.¹⁰ Approximately 11-15% is protein bound. C_{max} and AUC increase in a dose-proportional manner. C_{max} at doses of 0.15 mg/kg, 0.30 mg/kg and 0.50 mg/kg was reported to be 117, 239 and 392 ng/mL, respectively. AUC_{0-24h} at doses of

0.15 mg/kg, 0.30 mg/kg and 0.50 mg/kg was reported to be 175, 362, and 582 ng·h/mL. The half-life ($t_{1/2}$) in healthy volunteers was approximately 6 to 9 hours, and it does not appear to be related to the dose or route of administration.⁹

Figure 1. Structure of methylnaltrexone.¹⁰



Methylnaltrexone undergoes minimal metabolism (less than 10% of the administered dose).⁹ Its major metabolites are methyl-6-naltrexol isomers and methylnaltrexone sulfate. An insignificant amount of the administered dose is metabolized to naltrexone. Methylnaltrexone appears to be excreted mainly as the unchanged drug. About half the dose is excreted renally. There appears to be a significant amount of active tubular secretion of methylnaltrexone. A little less than half

the dose is excreted fecally via hepatobiliary secretion and/or gastrointestinal reflux of unchanged drug.⁹

Pivotal Studies

Two pivotal studies^{9,11} led to the approval of methylnaltrexone for opioid-induced constipation in patients with advanced illness. Patients in both studies had a terminal disease, such as cancer or some other end-stage disease (for example, cardiovascular disease, chronic obstructive pulmonary disease, emphysema, Alzheimer's disease, or dementia) and were receiving palliative care and chronic opioid therapy for pain. The primary outcome in both studies was rescue-free laxation (bowel movement without the use of rescue laxatives) within 4 hours of the initial dose of methylnaltrexone. One of the studies¹¹ had a co-primary outcome: rescue-free laxation within 4 hours after two or more of the first four doses. The rates of rescue-free laxation within 4 hours of the initial dose in the double-blind phases of these two pivotal studies are shown in Table 1.

Thomas et al¹¹ conducted a two-phase study. In the double-blind phase, the investigators randomized 133 adult patients (mean age approximately 71 years, range 34-98 years) with opioid-induced constipation who had received conventional laxatives for 3 or more days without relief to 0.15 mg/kg subcutaneous methylnaltrexone (n = 62) or placebo (n = 71) every other day for 2 weeks. If patients had not experienced three

laxations without the use of rescue laxatives by day 8, the dose could be doubled to 0.3 mg/kg. Following this phase, eligible patients entered a 3-month open-label phase and could receive subcutaneous methyl-naltrexone as needed up to every 24 hours. The initial dose during this phase was 0.15 mg/kg and subsequent

the double-blind phase and 48-52% in those who had received placebo.

In the double-blind phase, a similar number of patients in each group had at least one adverse effect. Most adverse effects were rated the investigators as mild or moderate. Statistical analysis on the adverse

Table 1. Rates of rescue-free laxation within 4 hours of initial dose in double-blind phases of pivotal studies.^{9,11}

Reference	MNTX 0.15 mg/kg	MNTX 0.30 mg/kg	Placebo	P-value
Thomas 2008 ¹¹	30/62 (48%)	–	11/71 (15%)	p < 0.001
Unpublished ⁹	32/55 (58%)	39/47 (62%)	17/52 (14%)	p ≤ 0.0001

MNTX = methyl-naltrexone

doses could be increased to 0.30 mg/kg if laxation did not occur within 4 hours or decreased to 0.075 mg/kg if adverse effects occurred.

In the double-blind phase, rescue-free laxation occurred within 4 hours of the first dose in 48% of patients in the methyl-naltrexone group compared to 15% of patients in the placebo group (p < 0.001). The proportion of patients who experienced rescue-free laxation within 4 hours after two or more doses was similar and was significantly higher in the methyl-naltrexone group (52%) compared to the placebo group (8%, p < 0.001). The median time to laxation was significantly less in the methyl-naltrexone group (6.3 hours) compared to placebo (> 48 hours, p < 0.001). Overall, 287 doses of methyl-naltrexone were administered and rescue-free laxation occurred in 45% of patients within 4 hours of a dose, and 277 doses of placebo were administered with rescue-free laxation occurring in 11% of patients within 4 hours of a dose.

Secondary outcomes included time to laxation, stool consistency, difficulty of laxation, constipation-associated distress, patient perception of improvement in bowel status, pain scores and opioid-withdrawal symptoms. Stool consistency improved in a similar percentage of patients in both groups. Difficulty of laxation and constipation-associated distress improved more in the methyl-naltrexone group. The majority of patients in the methyl-naltrexone group reported that their bowel status had improved, while the majority of patients who received placebo reported that their bowel status was unchanged. There were minimal changes in pain scores from baseline, and opioid-withdrawal symptoms did not increase from baseline.

Eighty-nine patients continued to the open-label phase during which they received the drug as needed up to every 24 hours. During this phase, rescue-free laxation rates in months 1 through 3 were 45-58% in patients who had received methyl-naltrexone during

effects was not reported. In the methyl-naltrexone group, the most common adverse effect was abdominal pain. Adverse events occurring more frequently in the methyl-naltrexone group compared to the placebo group were abdominal pain (17% versus 13%), flatulence (13% versus 7%), increase in body temperature (8% versus 3%), dizziness (8% versus 3%), and diarrhea (6% versus 4%). No serious events that were likely related to methyl-naltrexone occurred. Similar percentages of patients in each group discontinued due to adverse effects (6% in the methyl-naltrexone versus 7% in the placebo group). No methyl-naltrexone-related deaths occurred.

The other pivotal study has not been published at the time of this writing, but it is described in the FDA's medical review.⁹ This study was composed of three phases. Initially, 154 patients (mean age 65.3 years, range 21-100 years) were included in a one-day, double-blind placebo-controlled period. Patients were randomized to receive one dose of subcutaneous methyl-naltrexone 0.15 mg/kg (n = 47), 0.30 mg/kg (n = 55) or placebo (n = 52). Twenty-four hours after this dose, 136 of these patients continued on to a 4-week open-label period. The initial dose during this period was 0.15 mg/kg daily and patients could receive subsequent doses of 0.075 mg/kg, 0.15 mg/kg, or 0.30 mg/kg given daily as needed. This study had a 3-month extension phase. Twenty-seven patients entered this phase, and 21 ultimately received subcutaneous methyl-naltrexone starting at the dose that they received last in the open-label phase. As in the open-label phase, doses in the extension phase could be adjusted to 0.075 mg/kg, 0.15 mg/kg, or 0.30 mg/kg and given daily as needed.

During the one-day double-blind phase, rescue-free laxation occurred in 62% of patients in the 0.15 mg/kg group, 58% of patients in the 0.30 mg/kg group and 14% of patients in the placebo group (p <

0.001). A secondary endpoint was rescue-free laxation within 24 hours of the initial dose, which occurred in 68% of patients in the 0.15 mg/kg group and in 64% of patients in the 0.30 mg/kg group compared to 27% of patients in the placebo group ($p \leq 0.0001$ for each methylnaltrexone group versus placebo).

In the open-label phase, rescue-free laxation occurred within 4 hours of the first dose in 62% of

Adverse Effects

In double-blind, placebo-controlled clinical studies of subcutaneous methylnaltrexone, the adverse effects judged to be caused by methylnaltrexone were gastrointestinal effects and dizziness.¹⁰ The adverse effects and frequency are shown in Table 2. Adverse effects led to discontinuation in 5 patients (3%) in the methylnaltrexone groups and in 5 patients (4.1%) in

Table 2. Adverse effects from all doses in double-blind phases of pivotal studies.¹⁰

Adverse Effect	Methylnaltrexone (n = 165)	Placebo (n = 123)
Abdominal pain	47 (28.5%)	12 (9.8%)
Flatulence	22 (13.3%)	7 (5.7%)
Nausea	19 (11.5%)	6 (4.9%)
Dizziness	12 (7.3%)	3 (2.4%)
Diarrhea	9 (5.5%)	3 (2.4%)

patients who had been in the 0.15 mg/kg double-blind group, in 52% of patients who had been in the 0.30 mg/kg double-blind group, and in 54% of patients who had been in the placebo double-blind group (p values not reported). By 24 hours, rescue-free laxation had occurred in 76% of patients who had been in the 0.15 mg/kg double-blind group, in 59% of patients who had been in the 0.30 mg/kg double-blind group and in 71% of patients who had been in the placebo double-blind group (p values not reported).

Efficacy data from the extension phase was pooled with data from the double-blind and open-label phases in the FDA's medical review, so specific information is unavailable at this time. During the extension phase, a 73-year-old patient receiving methylnaltrexone died after experiencing severe diarrhea, dehydration, and cardiovascular collapse, which was considered by the investigators as probably due to methylnaltrexone. She had completed the single-dose double-blind phase and had received 4 doses (one 0.15 mg/kg dose and three 0.30 mg/kg doses) during the open-label phase. Additional safety data from this study were pooled with other studies in the FDA's medical review, and the specifics from this trial have not been published.

the placebo groups.⁹ In the methylnaltrexone groups, 2 patients discontinued due to abdominal pain, 1 discontinued due to abnormal bowel sounds, 1 discontinued due to asthenia and 1 discontinued due to an unspecified condition.⁹

Contraindications, Warnings and Precautions

Methylnaltrexone is contraindicated in patients with known or suspected gastrointestinal obstruction. If patients develop severe or persistent diarrhea, methylnaltrexone should be discontinued.¹⁰

Dosing, Administration, and Cost

Methylnaltrexone should be administered subcutaneously in the abdomen, thighs or upper arms.¹⁰ Dosing is weight-based (Table 3). The usual schedule is one dose every other day, as needed. If needed more frequently, a maximum of one dose in a 24-hour period may be administered. Methylnaltrexone is available in single-use vials containing 12 mg/0.6 mL. Patients may self-administer the drug. The cost is approximately \$50/vial.¹²

Special Populations

Methylnaltrexone is in pregnancy risk category B.¹⁰ There has been no evidence of impaired fertility or harm to the fetus in animals, and there are no adequate, well-controlled studies in pregnant women. The drug should be used during pregnancy only if clearly needed. In humans, the effects of methylnaltrexone on

Table 3. Weight-based dosing of methylnaltrexone.¹⁰

Patient Weight		Dose
Pounds	Kilograms	
< 84	< 38	0.15 mg/kg
84 to < 136	38 to < 62	8 mg
136 to 251	62 to 114	12 mg
> 251	> 114	0.15 mg/kg

the mother, fetus, duration of labor and delivery are unknown. In animals no effects were seen. Methyl-naltrexone is excreted in the milk of lactating rats, but it is unknown whether it is excreted in human milk. The drug should be used with caution in nursing women.¹⁰

The safety and efficacy of methyl-naltrexone have not been established in pediatric patients.¹⁰ Geriatric patients were included in phase 2 and 3 double-blind studies and no difference in efficacy or safety was seen. No dosage adjustment in the elderly is recommended.¹⁰

No dosage adjustment in patients with mild or moderate renal impairment is necessary.¹⁰ In patients with severe renal impairment (creatinine clearance <30 mL/min), the dose should be reduced by one-half.¹⁰ No studies have been performed in dialysis patients.

No dosage adjustment in patients with mild or moderate hepatic impairment (Child-Pugh Class A and B) is necessary.¹⁰ No studies have been performed in patients with severe hepatic impairment.

Drug Interactions

Based on the results of preclinical studies, methyl-naltrexone is not believed to induce or inhibit CYP450 isozymes in humans. For this reason, methyl-naltrexone has a low probability of drug-drug interactions.⁹ The low protein binding is also suggestive of low potential for drug-drug interactions. Since methyl-naltrexone appears to be actively secreted by the kidneys, there is a possibility that it could interact with drugs that are actively secreted renally.¹⁰ However, this potential has not been investigated in humans.

Conclusion

Methyl-naltrexone is an important advance in the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care and who have not responded to conventional therapy. Not only is it the first drug in its class, it is also the first drug ever to receive FDA approval for this condition. Although the drug is given subcutaneously, patients may self-administer it. It does not cross the blood-brain barrier, so it does not affect the efficacy of opioid analgesics and does not appear to be associated with withdrawal effects. Mild gastrointestinal effects and dizziness appear to be the most common adverse effects, and they rarely led to discontinuation in clinical trials.

Methyl-naltrexone should be reserved for second-

line therapy if laxatives alone are ineffective. The drug was approved for use in palliative care based on two pivotal studies that enrolled a combined total of fewer than 300 patients and lasted less than 4 months — with a 2-week double-blind phase in one study and a 1-day double-blind phase in the other — so it remains to be seen whether the efficacy and safety record observed in these trials will be validated in a larger patient population for a longer period of time.

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Vicki Kee is a 1989 graduate of the University of Alabama at Birmingham (B.A. in English) and a 1999 graduate of Samford University School of Pharmacy (Pharm.D.). She completed a drug information residency at Idaho State University College of Pharmacy in 2003 and then joined *IDIS*. In 2005 she became a Board Certified Pharmacotherapy Specialist.

Vicki is a contributing author to the *World of Drug Information* newsletter, assists with answering drug information inquiries made to the Iowa Drug Information Network (IDIN), teaches drug information to pharmacy students and indexes journal articles for inclusion into the *IDIS* database.

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ACPE# 107-999-08-093-H01-P (0.1 CEU/1 Hr.)

Volume: 19 Issue: 3 SEPTEMBER 2008

Title of Educational Activity

METHYLNALTREXONE FOR OPIOID-INDUCED CONSTIPATION IN PALLIATIVE CARE

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I hereby certify that I have taken this test:

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(circle the correct answer)

1. Methylnaltrexone is an antagonist of which one of the following opioid receptor classes?
 - a. Delta (Δ)
 - b. Kappa (K)
 - c. Mu (μ)
 - d. Pi (π)
2. All of the following cross the blood-brain barrier EXCEPT:
 - a. Naloxone
 - b. Naltrexone
 - c. Methylnaltrexone
 - d. Nalmefene
3. Methylnaltrexone acts almost exclusively in which one of the following?
 - a. Central nervous system
 - b. Gastrointestinal tract
 - c. Respiratory system
 - d. Urinary tract
4. Which one of the following is in the same drug class as methylnaltrexone?
 - a. Alvimopan
 - b. Tegaserod
 - c. Alosetron
 - d. Metoclopramide
5. In the double-blind phases of the two pivotal studies, rescue-free laxation occurred within 4 hours of the initial dose in what percentage of patients receiving methylnaltrexone?
 - a. 33-45%
 - b. 48-62%
 - c. 74-79%
 - d. 82-94%
6. Which one of the following is the recommended dose of methylnaltrexone?
 - a. 0.15 mg/kg
 - b. 8 mg
 - c. 12 mg
 - d. 0.15 mg/kg, 8 mg or 12 mg, depending on the weight of the patient

7. The usual schedule of methylnaltrexone is one dose _____.
 - a. Twice a day as needed
 - b. Every other day as needed
 - c. Once weekly
 - d. Once a month
8. The dose of methylnaltrexone should be reduced by one-half in which one of the following?
 - a. Patients with severe renal impairment
 - b. Geriatric patients
 - c. Patients with severe hepatic impairment
 - d. Pregnant patients
9. Which one of the following has been reported to interact with methylnaltrexone?
 - a. Carbamazepine
 - b. Rifampin
 - c. Cimetidine
 - d. None of the above
10. Which one of the following is a common adverse effect of methylnaltrexone?
 - a. Cough
 - b. Constipation
 - c. Urinary retention
 - d. Abdominal pain

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Overall quality	5	4	3	2	1
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	5	4	3	2	1
Important to pharmacists	5	4	3	2	1
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FDA Approvals
June 2008 – August 2008

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the *IDIS* database.

Generic Name Trade Name (Review Classification)	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)	Indication/Use Dosage Form	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Clevidipine Butyrate <i>Cleviprex</i> (S)	Medicines Co. (Aug. 1, 2008)	CLEVIDIPINE 24120448 (9 citations)	Reduction of blood pressure when oral therapy is not feasible or desirable. Intravenous Inject	Hypertension 401.
Difluprednate <i>Durezol</i> (P)	Sirion Therap. (Jun. 23, 2008)	DIFLUPREDNATE 84060028 (1 citation)	Topical treatment of inflammation and pain associated with ocular surgery. Ophth Emulsion	Disorder, Eye NEC 379. Aftercare NEC V58.8 Pain NEC 780.91
Fluorescein Sodium <i>Ak-Fluor</i> (S)	Akorn (Aug. 8, 2008)	FLUORESCEIN 52360006 (56 citations)	Diagnostic angiography or angiography of the retina and iris vasculature. Injection	Angiography, Eye 95.12
Romiplostim <i>Nplate</i> (BIOL)	Amgen (Aug. 22, 2008)	ROMIPLOSTIM 95000277 (18 citations)	Thrombocytopenia. Subcutaneous Inject	Thrombocytopenia, Primary 287.3
Tetrabenazine <i>Xenazine</i> (P,O)	Xenazine (Aug. 15, 2008)	TETRABENAZINE 28160841 (31 citations)	Chorea associated with Huntington's disease. Oral Tablet	Huntington's Chorea 333.4

Review Classification:

S = Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs

AA = Accelerated Approval

FT = Fast Track

P = Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease

BIOL = Biological

O = Orphan drug



Dr. Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and (Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the *IDIS* database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.

Selected Bibliography

Clevidipine

Levy JH, Mancao MY, Gitter R, et al. Clevidipine effectively and rapidly controls blood pressure preoperatively in cardiac surgery patients: the results of the randomized, placebo-controlled efficacy study of clevidipine assessing its preoperative antihypertensive effect in cardiac surgery-1. *Anesth Analg*. 2007; 105:918-925. (**IDIS** Article Number 583791) *Efficacy and tolerability of clevidipine in treating preoperative hypertension was assessed in this randomized, double-blind, placebo-controlled multicenter trial that included 105 patients whose systolic blood pressure was ≥ 160 mm Hg. Treatment failure was defined as failure to achieve $\geq 15\%$ reduction from baseline of systolic pressure, or discontinuance of the study drug for any reason. Patients were randomized to receive infusions of clevidipine 0.4-0.8 $\mu\text{g}/\text{kg}/\text{min}$, or placebo, for at least 30 minutes. Results showed that patients who received clevidipine had a 92.5% rate of treatment success, and significantly lower rate of treatment failure (7.5%, 4 of 53) compared with the placebo group (82.7%, 43 of 52; $p < 0.0001$), and clevidipine reached the target of reducing systolic pressure by $\geq 15\%$ at a median of 6.0 minutes (95% CI 6-8 mins). Clevidipine was well tolerated, although heart rate increased modestly during infusion.*

Romiplostim

Kuter D, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomized controlled trial. *The Lancet*. 2008; 371:395-403. (**IDIS** Article Number 590271) *Two parallel trials were conducted with 63 splenectomized and 62 non-splenectomized immune thrombocytopenic purpura patients, with mean platelet counts of $30 \times 10^9/\text{L}$ or less, randomized 2:1 to romiplostim or placebo given subcutaneously weekly for 24 weeks. Results showed that in the splenectomized patients, 16 of 42 who received romiplostim versus none of 21 given placebo achieved a durable platelet response, (proportional difference in patients responding 38% [95% CI 23.4-52.8], $p = 0.0013$), and in the non-splenectomized patients 25 of 41 given romiplostim versus one of 21 given placebo (56% [95% CI 38.7-73.7], $p < 0.0001$). Adverse events were similar in patients given romiplostim and those given placebo, and antibodies against romiplostim or thrombopoietin were not found.*

Tetrabenazine

Marshall FJ, Walker F, Frank S, et al. Tetrabenazine as antichorea therapy in Huntington disease. *Neurology*. 2006; 66:366-372. (**IDIS** Article Number 549552) *A total of 84 Huntington disease patients were randomized to receive tetrabenazine ($n = 54$) or placebo ($n = 30$) in this 12 week study. Dosing for tetrabenazine was increased over a 7-week period to a maximum of 100 mg/day or until desired effects occurred, or until intolerable adverse effects. The primary outcome, change from baseline in the chorea score, was based on the Unified Huntington's Disease Rating Scale (UHDRS). Patients treated with tetrabenazine showed a reduction of 5.0 units in severity of chorea, compared with a reduction of 1.5 units in patients treated with placebo, (adjusted mean effect size = -3.5 ± 0.8 UHDRS units [mean \pm SE]; 95% CI: -5.2, -1.9; $p < 0.0001$). In the study group, 5 patients withdrew and 5 patients had serious adverse events, compared with one patient withdrawal and no serious adverse events in the placebo group.*

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