date AO drugs developed for several conditions.[30–34] Some of these studies have used modification of the 5′ and 3′ ends, with 2′-O-methoxy ethyl–modified ribose to make the drugs more resistant to degradation by nucleases. AOs can prolong the intrinsic clotting pathway (activated partial thromboplastin time) and increase complement split products in the monkey, but this appears to be dose dependent, with clinically significant levels occurring at relative high plasma peak concentrations (>50 μg/mL).[35] Human phase 1 safety studies have shown concentration-dependent effects on coagulation and complement, with the maximum tolerated dose by 24-hour infusion being approximately 20 mg/kg.[36] The observed adverse effects appear to be transient. Similar to other 2′-substituted AOs, the most prominent end-organ finding for phosphorothioate AOs in the monkey has been the presence of granules in the proximal tubular epithelial cells of the kidney, most likely from the uptake by phagocytosis of filtered oligonucleotide.[37] Regarding applications to DMD, phosphorothioate chemistries (2′OMe) have the great advantage of extensive preclinical and clinical experience.

Morpholino

This is the chemistry of choice in the AVI BioPharma DMD program (AVI BioPharma, Bothell, WA). The key advantage of the morpholino chemistry compared with phosphorothioate is the superior therapeutic window. Morpholino AOs have been dosed i.v. in monkeys to 320 mg/kg per week and in rodents to 960 mg/kg per week, with no evidence of dose-limiting toxicities.[38] As noted later, the 2′OMe drug PRO051 showed proteinuria at 6 mg/kg per week using s.c. doses in patients with DMD, whereas a similar morpholino drug showed no proteinuria at doses to 320 mg/kg per week using i.v. delivery in monkeys.

The major disadvantages are the much lower clinical experience with morpholino chemistry. There have been three clinical trials completed involving 39 patients with morpholino antisense, compared with 40 trials and 2000 patients in completed trials with other antisense AO chemistries (*http://www.clinicaltrials.gov*).

Phosphorodiamidate morpholino oligomers (PMOs) are a class of backbone modification that has a morpholino ring as a replacement for the furanose, with phosphorodiamidate linkage connecting the morpholino nitrogen atom with the hydroxyl group of the 3′ side residue (Figure 3). This backbone modification sets this class of AOs apart from most other modifications, and the synthesis of these AOs is unique. Until recently, this chemistry was not in the public domain for therapeutic applications. As a result, only modest progress has been made in improving the purity, capacity, and cost of goods for these AOs.

AOs synthesized from morpholinos retain high sequence specificity and strong binding to the target RNA. They are sufficiently dissimilar from native RNA and DNA in that they are not recognized by host RNA or DNA or degrading enzymes, thus making them more stable. In animal models, AOs synthesized from morpholinos (PMOs) do not cause complement activation at high serum concentrations after repeated (weekly) i.v. administration (approximately 1 g/kg per week i.v.; AVI BioPharma poster, *http://www.avibio.com/wp-content/uploads/2010/10/AVI-4658-WMS-Preclin-Poster-101510.pdf*, last accessed March 1, 2011). PMOs are highly water soluble, are not subject to metabolic degradation, and do not activate the toll-like receptors, the interferon system, or the NF-κB–mediated inflammation response.[39]

Toxicity studies have been performed in both mouse (12 weekly i.v. or s.c. injections to 960 mg/kg per dose) and monkey (12 weekly i.v. or s.c. injections to 320 mg/kg per dose). No evidence of liver or kidney dysfunction was seen, although there was histological evidence of accumulation in the proximal renal tubules, a finding seen with most AOs. Clinical trials of PMOs are under way in the UK and are about to begin in the US; thus, clinical safety data for DMD are limited.

Additional Chemistries and Technologies for Exon Skipping

Although the approaches previously described are promising, alternative strategies are being developed to address some potential limitations. Alternatives include the development of methods and chemistries to i) increase potency to reduce the amount of drug that will need to be manufactured and delivered to patients; ii) permit delivery to nonskeletal muscle target tissues, such as the heart; and iii) mitigate the need for repeated parenteral administration (eg, weekly or monthly i.v.).

One approach is to increase the charge of the AO through addition of residues along the backbone or at either end. Examples of modifications of the end of the AO include the peptide-modified PMO or morpholino[40] and guanidium dendrimer (vivo morpholino).[41] Another approach is to add targeting peptides (ie, small amino acid sequences that can interact with the muscle fiber membrane).[42,43]

Although each of these modifications to the backbone increases potency, the modifications also tend to bypass the holes in membrane delivery that unstable DMD membranes afford and, thus, lose this disease-specific advantage in DMD. They also tend to increase toxicity because they may bind to plasma proteins or cell surface proteins on nonmuscle cells (or vasculature or blood cells) and generate undesired off-target effects. Although alternative chemistries will be a continued focus for research, it is likely that efficacy in DMD will first be proved using the existing PMO and 2′OMe chemistries.

Another alternative approach is to perform exon skipping using gene therapy instead of AOs.[44–46] Herein, specific mRNA splicing molecules (ie, U7 or U1 RNA) are designed to splice out extra exons; these customized U7 drugs are coded within gene therapy viral vectors. The muscle is infected with the virus, the U7 drugs are expressed, and the drugs work efficiently at driving the desired in-frame spliced products. A critical advantage of the U7 approach is that one treatment may last a lifetime because the gene therapy vectors seem stable in muscle and continue to express the U7 RNA. A disadvantage of this approach is that it requires

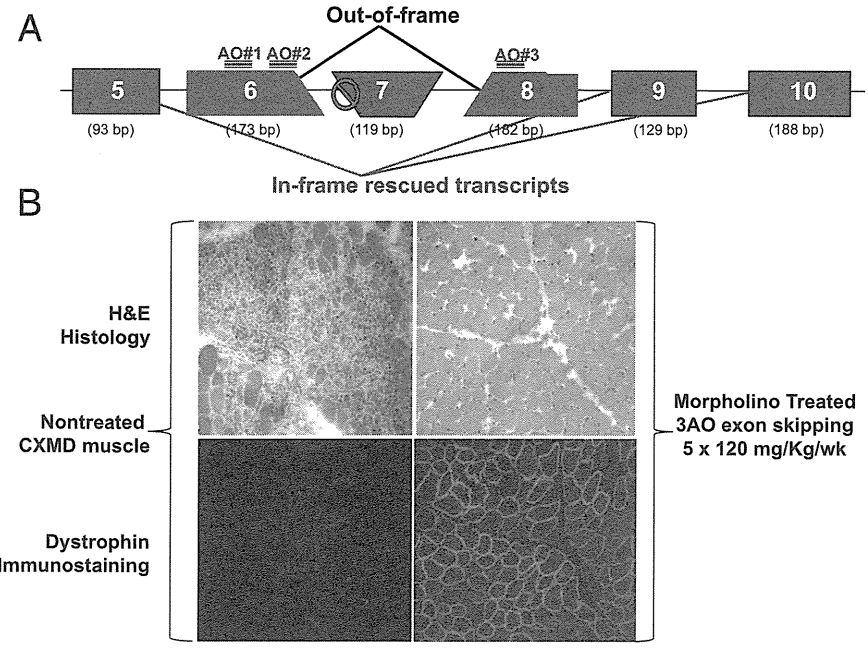

Figure 4. Delivery of multiple PMO drugs to a dog model of DMD skips multiple exons and results in *de novo* dystrophin production. **A:** Schematic of dog gene structure. The sporadic golden retriever dystrophin gene mutation is a splice-site mutation of exon 7 (red symbol). This forces the exclusion of exon 7, whereby the dystrophic dog muscle splices exon 6 to 8, but these exons do not share the same reading frame (out of frame). AOs covering exons 6 and 8 were designed (AOs 1, 2, and 3) to block inclusion of exons 6 and 8, leading to in-frame rescued transcripts (exons 5 to 9 or 5 to 10). **B:** Histological features and matched dystrophin immunostaining of AO-treated dystrophic dogs (**right**) and controls [nontreated canine X linked muscular dystrophy (CXMD) muscle; **left**]. Nontreated muscle shows necrosis of myofibers and inflammatory cell infiltration, whereas AO-treated muscle shows no inflammation or necrosis. Dystrophin protein is absent in the nontreated muscle, whereas the AO-treated muscle shows high amounts of membrane dystrophin, comparable to healthy muscle. Adapted with permission from Yokota et al (copyright 2009, John Wiley & Sons).[56]

viral gene therapy; as previously noted, gene therapy of DMD has faced persistent hurdles of immune response, viral production, and systemic delivery.[47]

Evidence for Efficacy of AO Exon Skipping: Preclinical and Clinical Studies

Animal Studies

The premise for exon skipping in DMD has been well studied in the *mdx* mouse model. In the early part of this decade, several laboratories established the fact that delivering sequence-specific AOs can induce exon skipping, which reestablishes the reading frame of dystrophin mRNA in myogenic cell cultures.[19,48–50] After these early findings, the AOs could be delivered via i.m. injection and could induce dystrophin expression to near–normal levels in most muscle fibers; this was accompanied by functional improvement.[51] Most recently, systemic delivery of AOs by i.v. injections can induce exon skipping and dystrophin expression up to levels found in healthy muscle. In addition, after three i.v. injections at weekly intervals, enhanced dystrophin expression was detected in every skeletal muscle examined.[52] Regarding dose-response and dosing schedules, single injections at a high dose (3 g/kg) show robust dystrophin expression and relatively long persistence of protein rescue.[53] These preclinical data suggest that i.v. delivery might show good efficacy at a frequency of three to four doses per year, rather than the weekly doses used in most current preclinical and clinical studies.

An oft-quoted adage is that academic medicine has generated thousands of highly efficacious mouse drugs and far fewer effective human drugs. Demonstration of efficacy in a large animal model typically engenders more confidence in human applications. Therefore, work[54,55] has been performed in the dog model of DMD that has a mutation in exon 7 of the dog dystrophin gene. Dogs with DMD represent a particularly stringent test of exon skipping, in that: i) they typically show rapidly progressive disease, often leading to death by 6 months; ii) the nature of the dog mutation requires skipping of two exons to bring the transcript back into frame; and iii) because the dog deletion is near the beginning of the dystrophin protein (actin binding site), this may be more biochemically disabling to the protein than more central deleted regions (Figure 4). In these studies, three morpholino AO drugs were codelivered to dogs with DMD to achieve exon skipping, using high doses of up to 200 mg/kg i.v. per week.[56] Given the size of the dogs, these studies required production of a large amount of AO drug.

Despite the stringency of the model, all of the three dogs tested showed stabilization or improvement of multiple functional, imaging, and histological parameters (Figure 4). Dystrophin production was increased to an average of approximately 20% in all skeletal muscles, and no toxicities were observed despite the high cumulative exposure. The dystrophin amounts varied considerably from muscle to muscle, and, consistent with murine studies, systemic delivery to the heart was poor.

Clinical Studies

The first human studies were published from a private/public partnership in Leiden, the Netherlands, between the university and Prosensa Therapeutics.[57] The AO drug, PRO051, was against exon 51 of the human dystrophin *(DMD)* gene and used phosphorothioate (2′OMe) chemistry (Figure 1). In a phase 1 safety study completed in 2007, single i.m. doses of PRO051 were safe and well tolerated in four patients with DMD who were aged 10 to 13 years and were selected on the basis of mutational

status, muscle condition, and positive response to exon skipping 51 in their cultured cells *in vitro*. A biopsy specimen of the injection site that was obtained 4 weeks later showed evidence of *de novo* dystrophin expression.

Data from an investigator-initiated clinical trial in London, UK, using a single i.m. injection of morpholino AO (AVI BioPharma) were published in 2009.[58] The investigators used an AO sequence that was similar, but not identical, to that used in the previous Dutch trial but switched to the newer morpholino chemistry. In this phase 1 study, AVI-4658 was given to seven patients with DMD (aged 12 to 18 years) as an i.m. injection in the extensor digitorum brevis. Two boys received a low dose of 0.09 mg in 900 μL, and five boys received 0.9 mg in 900 μL. Each boy received a saline injection in the contralateral extensor digitorum brevis. Muscle biopsy specimens were obtained before treatment and at 3 or 4 weeks and examined for dystrophin production. AVI-4658 was well tolerated, and no dose-limiting toxicities were observed. Treated patients had evidence of induced dystrophin production in a dose-responsive manner.

In both i.m. studies, the amount of dystrophin in treated muscle, measured by immunoblot, was low (approximately 1% to 5%) versus levels in healthy muscle. Although immunoblotting is a good method for determining the average levels of dystrophin in the tissue, it has less sensitivity compared with dystrophin immunostaining, which is able to identify individual fibers expressing relatively low levels of dystrophin. Work is ongoing to evaluate and standardize the optimal methods for use in clinical trials. In addition, the amount of dystrophin expression that correlates with clinical response is not established. From early genotype-phenotype studies[59,60] of dystrophinopathies, dystrophin immunoblot levels >10% of normal may be necessary for clinical activity; neither i.m. study consistently reached this level.

An open-label dose-ranging study[61] of the PRO051 2′OMe drug in 12 patients was recently reported. Patients with DMD were given five weekly s.c. doses, ranging from 0.5 to 6 mg/kg, with muscle biopsy specimens obtained at both 2 and 7 weeks after the initiation of treatment. Both the 2- and 7-week biopsy specimens showed drug-induced dystrophin mRNA splicing and protein production, although the levels of dystrophin by immunoblot appeared lower than might be needed for altering clinical symptoms. There was no clear dose-response relationship between dystrophin immunostaining and drug doses. All patients were then enrolled into a 12-week extension study using the peak dose (6 mg/kg per week). At the conclusion of the extension study, patients seemed to perform better on a 6-minute walk test, suggesting clinical efficacy. Because biopsy specimens were not obtained after the 12-week extension study, it was not possible to correlate molecular efficacy with apparent clinical efficacy; and because the study was open label and not placebo controlled, the improvement in functional outcomes needs to be interpreted cautiously. Nevertheless, this study provided sufficient evidence for GlaxoSmithKline to initiate a 1-year, phase 3, blinded placebo-controlled study of 6 mg/kg per week s.c. dosing in 180 patients; the study enrolled patients at 14 sites in seven countries as this article was being written (*http://clinicaltrials.gov/ct2/show/NCT01254019?term=duchenne&rank=4*, last accessed March 1, 2011).

A key issue for success of high-dose antisense drug delivery is the achievement of a balance of toxicity and efficacy (therapeutic window). As previously described, there are well-documented toxicities that limit human dosing to approximately 20 mg/kg, yet both mouse and dog studies suggest that ≥40 mg/kg may be required for sufficient dystrophin production. In the GlaxoSmithKline/Prosensa dose-ranging study, all 12 patients enrolled experienced proteinuria and an elevated urinary α1-microglobulin level at week 12 of the extension period, suggestive of kidney toxicity. Renal proximal tubuli accumulate oligonucleotides through drug reabsorption, and it will be important to monitor kidney toxicity in the ongoing 12-month phase 3 study.

AVI BioPharma has performed a dose-escalation study in the UK with systemically administered AVI-4658. Although not yet published, data have been presented in press releases and at meetings. The study included six cohorts given 12 weekly i.v. doses, ranging from 0.5 to 20.0 mg/kg per dose. At the highest dose, one patient is reported to have *de novo* dystrophin production, with approximately 50% of fibers testing positive for dystrophin by immunostaining (AVI BioPharma news release, *http://investorrelations.avibio.com/phoenix.zhtml?c=64231&p-irol-newsArticle&ID=1433350&highlight=*, last accessed March 1, 2011); however, this likely translates to approximately 20% of total dystrophin muscle content by immunoblotting. The response of patients to a similar dose has been variable, and large interpatient variability may become a theme in exon skipping. There are at least two likely reasons for differences in interpatient response to a similar dose. First, i.v. doses are typically calculated based on weight of the patient (mg/kg); the peak serum dose, at which the drug can permeate through the leaky DMD myofiber membranes, may be more important. Thus, drug doses may need to be calculated more by body mass index or some other means of approximating blood volume, rather than simply by patient weight. Second, the *de novo* dystrophin produced by exon skipping is Beckerlike (not normal); researchers have observed that there can be remarkable interpatient variability in muscle dystrophin content, despite patients having the same in-frame deletion. For example, patients with Becker dystrophy who share a common exon 45 to 47 deletion can vary widely in the amount of dystrophin in their muscle by immunoblot and the severity of the histopathological features (Table 1).[62]

The preclinical and clinical data available thus far suggest that exon skipping may hold significant promise as a candidate treatment for DMD (although the response may be variable). However, these studies are early and clinical development is ongoing. Prosensa, in partnership with GlaxoSmithKline, has announced work on AO, targeting additional exons. AVI has an investigational new drug with the Food and Drug Administration and is expected to begin enrolling patients in trials in the US in 2011.

Table 1. Variability in Dystrophin Amount and Severity of Histopathological Features in Patients with Becker Muscular Dystrophy Who Share the Same In-Frame Deletion

Patient no.	Age at biopsy (years)	CPK level (U/L)	Histopathological features (severity of dystrophy)	Immunoblot (%)	Immunostaining
31	9	9760	Very mild	80	+++
32	7	NA	Moderately severe	5	++
33	1	3000	NA	50	++++
34	37	2844	Mild	20	+++
35	29	692	Mild	50	+++
36	38	NA	Severe	5	++
37	43	NA	Moderate	5	++
38	20	9543	Very mild	30	+++
39	13	NA	Moderately severe	80	++
40	59	NA	Moderate	30	++

Data are adapted from Kesari et al.[62] The gene mutation was an exon 45 to 47 deletion for all patients.
CPK, serum creatine phosphokinase; NA, not available; ++, moderate intensity; +++, moderately high intensity; ++++, high intensity (similar to normal controls).

Regulatory Pathway for AO Drugs

Exon skipping in DMD presents some unique challenges and may serve as a test case for personalized medicine, in which drugs are customized to a patient's genetic fingerprint. The exon 51 drug would only be applicable to relatively few patients with DMD. Indeed, drugs against five exons would be needed before even half of the patients with DMD could be treated with exon skipping. As each drug is developed, the number of patients available for that drug becomes smaller, for an already rare disorder. If each exon is considered a new drug requiring the full battery of toxicology and preclinical and clinical studies, then the time for development and costs represent a significant challenge. Some of the populations are so small that achieving statistical significance in a clinical trial will not be possible. Because some mutations will require simultaneous delivery of multiple drugs, as was the case with the dog model (Figure 4), the problem is compounded.

AO drugs in development for DMD have been granted Orphan Drug Designation by the Food and Drug Administration, which is designed to facilitate the development of these (and other) drug candidates.[63] This designation provides certain tax credit and marketing incentives to sponsors. Although Orphan Drug Designation does not change the requirements for drug approval, these drugs may also qualify for a 6-month priority review.[64] Although the challenges are significant (as previously described), at least two companies have launched clinical trials of AO products; these products will begin to define the regulatory path forward. Also, regulatory and scientific agencies, parent advocates, and academic researchers in the US and Europe are working to define the key issues and potential solutions in AO drug development for DMD.

One concept that has received some attention is based on an assumption that AOs of a given chemistry will have a common safety profile (preclinical and clinical) and that they will have a common pharmacokinetic profile. If this turns out to be the case, then cumulative data on the initial exon-specific drugs may allow a more streamline preclinical toxicology package. Also, if biomarkers, such as qualitative dystrophin expression, can be validated and correlated with clinical outcomes in initial trials, they could hypothetically be used in studies of later exon-specific drugs (particularly when a given mutation occurs in a few boys). After the first exon-specific drugs (eg, two drugs) are subjected to the standard battery of preclinical and clinical tests, using existing paradigms for drug approvals in rare life-threatening orphan diseases, subsequent exon-specific drugs (and perhaps multidrug combinations) would be approved, with a reduced battery of testing. This process reduces the cost and time to bring all exonic drugs to all patients with DMD. This concept is similar to the concept used in the annual release of the influenza vaccine. After approval of a given manufacturer's vaccine, in subsequent years, the seasonal vaccine (often with a composition that is different from that studied for initial approval) is released (approved) based on a smaller, but well-defined, set of parameters. Regardless of the pathway to approval, given that the number of boys with DMD available for study prelicensure will be limited, it is likely that postapproval studies and long-term follow-up of treated patients will be required.

Another issue in AO drug development for DMD is the selection of clinical trial end points based on an understanding of the natural history of DMD and (as previously discussed) standardized consensus methods for dystrophin protein measurement (biochemical outcome measures). The outcome measure that has previously been used for drug approval in other areas has been a 6-minute walk test. The TREAT-NMD European network has formed an international effort with the US Wellstone Center network to address clinical outcome measures in clinical trials, and publications are expected within the next year. One of the issues with the existing test is that it limits registration trials to ambulatory boys. Additional end points for boys in most need of treatment (nonambulatory) are needed, such that this group of patients can benefit from participation in clinical trials and so that nonambulatory boys will be included in the drug approval process.

Finally, approval of AO drugs for DMD will require refinements in production and potency. As previously mentioned, current estimations of the dose and regimen needed for treatment of a boy with DMD suggest that it

may involve ≥10 i.v. injections per year, with a cumulative annual dose of >10 g of AO drug. If we assume that these doses will be tolerated, the current production costs of morpholino drugs are high and the GMP production capacity is limited. 2′O-methyl chemistries are more widely available and less expensive. For morpholinos, one approach to decrease the high cost of production of large amounts of drug is to increase potency so that less drug is needed per patient. Some promising approaches to increase potency have been reported in mouse models, in which the AOs are modified to more efficiently enter cells or by codelivery of small molecules or nanoparticles that enhance AO uptake or splicing efficiency.[65–69] However, these drugs show new toxicities relative to the naked unmodified morpholino backbone; and it may be challenging to achieve an appropriate therapeutic window, despite the higher potency.

Premature Stop Codon Read Through: Gentamicin and Ataluren (PTC124)

In approximately 10% to 15% of boys with DMD, the disease is caused by a point mutation that causes a change in a triplet codon, so that it no longer codes for an amino acid but instead codes for a stop signal (nonsense codons UAA, UAG, or UGA). Translation of the dystrophin protein is prematurely stopped, and the short fragment is nonfunctional and/or degraded. A promising therapy for nonsense mutation DMD is ataluren (PTC Therapeutics, South Plainfield, NJ), an orally delivered small molecule designed to selectively induce ribosomal read through of premature stop codons but not normal termination codons. Ataluren was developed after gentamicin, an aminoglycoside, promoted read through in mammalian models and in the *mdx* mouse model but presented lack of potency and potential toxicity and administration issues.[70] These proof-of-concept experiments led researchers to use high-throughput screening methods to identify compounds that suppressed the early, but not normal, termination codons; and did not present the potency, toxicity, and administration issues associated with gentamicin. In *mdx* mice and muscle cell cultures from patients, ataluren, a nonaminoglycoside, promoted dystrophin production in primary muscle cells in humans and in *mdx* mice expressing dystrophin nonsense alleles. In addition, ataluren restored striated muscle function in *mdx* mice within 2 to 8 weeks of drug exposure.[71]

PTC Therapeutics has completed phase 1 clinical trials with ataluren and is finishing data analysis of its phase 2 studies. In phase 1, ataluren, delivered as a single or multiple doses, was safe and well tolerated and supported the initiation of phase 2 trials. A total of 62 healthy adult male and female volunteers were treated in phase 1.[72] In phase 2, 38 patients with DMD were given ataluren at one of three dose levels for 28 days. The drug was safe and well tolerated, with infrequent adverse events. Plasma concentrations correlating to activity in preclinical models were found at the middle and high doses. In addition, patients receiving ataluren showed qualitative increases in muscle dystrophin expression and reductions in serum creatinine kinase levels. These patients are being followed up in an open-label long-term safety study. In April 2008, a phase 2b study was initiated; by February 2009, the study had full enrollment by 173 patients with nonsense mutation DMD at 37 sites in 11 countries. This randomized, double-blind, placebo-controlled study had three arms, with approximately 55 patients per arm: placebo, low dose (10 mg/kg), and high dose (20 mg/kg) (PTC Therapeutics, *http://www.parentprojectmd.org/site/DocServer/2010-04-16_Final_Summary_of_Ataluren_Data_at_AAN.pdf?docID=9461*, last accessed March 1, 2011). Inclusion criteria permitted both steroid- and non–steroid-treated patients, a broad age range, and patients showing both Duchenne and Becker phenotypes. As a result, there was considerable range in disease progression. Neither drug-treated arm reached significance for the primary clinical outcome measure (a 30-m increase in the 6-minute walk test), although the low-dose cohort showed a promising trend toward clinical improvement. Dystrophin data have not been reported, and there have been no formal announcements of if or how clinical testing will continue.

Ataluren is in clinical trials for three other genetic disorders: cystic fibrosis (phase 3), hemophilia A and B (phase 2), and methylmalonic acidemia (phase 2). However, no new trials are listed for DMD; and the future of the drug in patients with muscular dystrophy is uncertain.

Summary

Small-molecule drugs to coax dystrophin production from mutated genes in DMD have emerged as the most promising molecular therapeutics. Both exon skipping using AOs and stop-codon read through (PTC124) have entered clinical trials, and preliminary results are encouraging. Both approaches are mutation specific and can be thought of as personalized medicine. Should clinical efficacy be demonstrated for exon skipping, then it will be important to have an efficient path for approval of other exon-specific drugs in the same class (chemistry) to bring this to most patients with DMD.

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抗うつ薬の開発

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はじめに

現在、うつ病は国民のこころの健康を脅かすパブリックヘルスの大きな問題となっている。その有病率は予想外に高く、障害調整生命年（Disability Adjusted Life Year：ＤＡＬＹ　障害をもちつつ暮らした時間と、死亡が早まることで失われた時間を統合した指標）の損失における最大の原因であり、今後二〇年間は増加傾向にあると推定されている。[1]

うつ病の治療の中心は薬物療法と精神療法である。ところが、現在用いられている治療では決して十分ではなく、治療の難しい症例も存在する。つまり、より効果的なうつ病の治療法を開発することにより、社会に大きな利益を与えることができるのである。しかし、あまたの化学物質の中から「抗うつ薬候補を発見した！」とある研究者が考えたとしても、その化学物質をすぐに患者に投与することはできない。

医薬品の開発においては、世界各国の医薬品承認審査の基準の合理化と標準化を目指し、日本・米国・ＥＵそれぞれの医薬品規制当局と産業界代表等で構成されるＩＣＨ（International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use：日米ＥＵ医薬品規制調和国際会議）が平成二（一九九〇）年に発足した（http://www.ich.org/）。ＩＣＨはこれまでにさまざまなガイドラインを公表しており、実際、抗うつ薬を含めた数多くの医薬品の国際共同開発がＩＣＨを背景に実施されるようになってきている。

わが国では、厚生労働省の承認なしに医薬品を製造販売することができない。また、薬事法に基づく医薬品の承認審査業務は、独立行政法人医薬品医療機器総合機構（ＰＭＤＡ）（http://www.pmda.go.jp/）が行っているが、医薬品の承認審査においては、薬学、医学、獣医学、理学、生物統計学などの専門課程を修了した審査員がその任に当たっている。抗うつ薬の開発においても例外ではない。

本稿では、抗うつ薬がどのように開発されるのかについて、抗うつ薬候補となる化学物質が初めて人間に投与されるまでに必要なプロセスを中心に概説する。

抗うつ薬は化学物質

現在、臨床で用いられている多くの医薬品のほとんどは、基本的に単なる化学物質である。そのため、抗うつ薬候補となる化学物質を開発

したいと思うのならば、まずその化学物質の特性をきちんと把握しなければならない。

また、その化学物質は、原薬（純粋な化学物質そのもの）のままで医薬品として用いられることは稀であり、多くの場合には添加物が配合され、顆粒や細粒、錠剤といった内服薬、あるいは、注射薬等の形に製剤化されて利用されるはずである。そのため、医薬品として開発される原薬についてのみならず、製剤についても、製造方法、規格および試験方法、安定性に関する情報を検討しなければならない。

表1　医薬品候補となる化学物質の品質に関する主な国内通知等

- 安定性試験ガイドライン（H15.6.3 医薬審発0603001）
- 新原薬及び新製剤の光安定性試験ガイドライン（H9.5.28 薬審422）
- 新有効成分含有医薬品のうち原薬の不純物に関するガイドライン（H14.12.16 医薬審査発1216001、H18.12.4 薬食審査発1204001）
- 新有効成分含有医薬品のうち製剤の不純物に関するガイドライン（H15.6.24 医薬審発0624001、H18.7.3 薬食審査発0703004）
- 医薬品の残留溶媒ガイドライン（H10.3.30 医薬審307）
- 新医薬品の規格及び試験方法の設定（H13.5.1 医薬審発568）
- 製剤開発に関するガイドライン（H18.9.1 薬食審査発0901001）
- 品質リスクマネジメントに関するガイドライン（H18.9.1 薬食審査発0901004、H18.9.1 薬食監麻発0901005）

これらの情報は、臨床現場での安全性を保証するために基本的な情報として、新医薬品の製造販売の承認を受けようとする場合においても必要となる。これらの情報の収集方法などについては、ＩＣＨガイドラインとして詳細に示されており、わが国では法令に準ずる国内通知等にて対応している（表1）。

規格試験項目としては、その化学物質の名称、構造式または示性式、分子式および分子量、基原、含量規格、性状（固体、液体、色など）、確認試験、示性値（吸光度、旋光度、pHおよび融点等の物理的化学的性質）、純度試験、水分含量（水分または乾燥減量）、強熱残分、灰分または酸不溶性灰分、製剤試験、特殊試験、その他の試験項目（微生物限度試験、原薬の粒子径を含む）、定量法等がある。安定性試験では、温度、湿度、光等のさまざまな環境因子の影響のもとでの品質の経時的変化を評価する。

非臨床試験――毒かクスリか？

次に必要なステップは、非臨床試験である。ある研究者が、「抗うつ薬になるかもしれない化学物質を発見した！」と考えたとしよう。しかし、医薬品のタマゴといってもいいこの化学物質は、文字どおり、毒にもクスリにもなりうる。そのため、その化学物質を初めて人間に投与する前には、毒ではなく「クスリ」として使える確からしさがどの程度かを値踏みするために、事前の厳密な手順に基づく検討が必要となる。

抗うつ薬候補となる化学物質を初めて人間に投与する前には、人間以外のモデル動物や培養細胞等を対象とする非臨床試験を実施しなければならないことが、薬事法において規定されている。医薬品の承認申請に必要な非臨床試験は、表2に示すとおり、薬効薬理試験、薬物動態試験、毒性試験の三種類に大きく分類される。

また、承認申請の添付資料として提出される

表2　医薬品の承認申請に必要な非臨床試験

- 薬理試験：効力を裏づける試験（薬効薬理試験）、副次的薬理（一般薬理）・安全性薬理、その他の薬理（薬力学的薬物相互作用）
- 薬物動態試験：吸収、分布、代謝、排泄
- 毒性試験：単回投与毒性、反復投与毒性、遺伝毒性、生殖発生毒性、その他の毒性

毒性試験や安全性薬理試験の結果は、信頼性が確保されていなければならない。このため、「医薬品の安全性に関する非臨床試験の実施の基準に関する省令」（平成九年三月二六日省令二一、平成二〇年改正省令一一四）が定められ、信頼性保証部門の設置、試験を外部施設に委託する場合の委託者の責務を明確にするとともに、試験施設の構造設備、標準業務手順書の作成、動物の管理、プロトコールや最終報告書の作成などが、この省令によって詳細に規定されている。非臨床試験に関する主な国内通知等については表3に示した。

表3　非臨床試験に関する主な国内通知等

- 医薬品の安全性に関する非臨床試験の実施の基準に関する省令（H9.3.26 省令21、H20 改正省令114）
- 医薬品の臨床試験のための非臨床安全性試験の実施時期について（H10.11.13 医薬審1019、H12.12.27 医薬審1831）
- 安全性薬理試験ガイドライン（H13.6.21 医薬審発902）
- 一般薬理試験ガイドライン（H3.1.29 薬新薬4）
- 薬物相互作用の検討方法について（H13.6.4 医薬審発813）
- 非臨床薬物動態試験ガイドライン（H10.6.26 医薬審496）
- 反復投与組織分布試験ガイダンス（H8.7.2 薬審442）
- トキシコキネティクス（毒性試験における全身的曝露の評価）試験（H8.7.2 薬審443）

(1) 薬効薬理試験

薬効薬理試験は、抗うつ薬候補となる化学物質の、人間での効能や効果を可能な限り事前に人間以外のモデル動物や培養細胞等を用いて裏づけておくための試験である。

選択的セロトニン再取り込み阻害薬（ＳＳＲＩ）やセロトニン・ノルアドレナリン再取り込み阻害薬（ＳＮＲＩ）、ノルアドレナリン作動性・特異的セロトニン作動性抗うつ薬（ＮａＳＳＡ）と分類されるような抗うつ薬は、すでに五〇年以上使用されている三環系抗うつ薬のもつ薬理作用の延長線上で開発された薬物である。そのため、こうした抗うつ薬の探索過程においては、非臨床試験として、モノアミン神経系に作用する抗うつ薬の予測妥当性に基づく試験が実施される。たとえば、各種神経伝達物質（ノルアドレナリン、アドレナリン、セロトニン、ドパミン、ヒスタミン等）の受容体等に対する作用を検討する *in vitro* 試験（いわゆる試験官内の試験）や、強制水泳試験、尾懸垂試験といった動物モデルを用いた試験が行われることが多い。

そのため、既存の抗うつ薬とは異なる、まったく新しい作用機序をもつ薬剤の評価に適した動物モデルの確立が、今後の大きなチャレンジとして希求されている。人間に投与した場合の効果を事前に裏づけておくためにも、うつ病の背景に存在する神経機構のよりいっそうの解明が必須であろう。

しかし、当然ながら、高度に発達した脳をもち、複雑な社会生活を営む人間の精神活動を、解剖学的にも機能的にも異なる脳を有する実験動物を用いて忠実に再現することは不可能である。そのため、その化学物質が本当に抗うつ薬候補であるかどうかは、最終的には人間に投与して初めて検証可能となる。

薬効薬理試験においては、既存薬との比較試験データやネガティブな結果が出た試験結果もよく吟味する必要がある。また、審査承認のための資料としては、申請の用法や臨床試験と同じ投与経路で実施することや、臨床用量との関係、作用機序の検討なども必要である。

安全性薬理試験には、生命維持をつかさどる器官系に対する試験も含まれる。

(2) 薬物動態試験

非臨床試験における薬物動態試験は、抗うつ薬候補となる化学物質の実験動物における動態（吸収、分布、代謝、排泄）を明確にするための試験である。動物で得られた全身的曝露と毒性試験の用量および時間経過との関係を明らかにするトキシコキネティクス（毒性試験における全身的曝露の評価）試験も、薬物動態試験として取り扱われる。

(3) 毒性試験

毒性試験は、抗うつ薬候補となる化学物質の、人間に投与した場合に生じうる毒性を可能な限り事前に、実験動物等を用いて確認しておくための試験である。具体的には、「単回投与毒性試験」「反復投与毒性試験」「遺伝毒性試験」「生殖発生毒性試験」が実施される。また、必要に応じ、「免疫毒性試験（一般毒性試験などで免疫毒性の兆候があった場合）」「局所刺激試験」「がん原性試験（臨床で六ヵ月以上投与される薬剤）」や「依存性試験（抗うつ薬を含む向精神薬など）」が実施される。

このように、非臨床試験において徹底的に調べ、人間に投与した場合の毒性や安全性を予測したうえでなければ、次のステップである臨床試験に移ることは許されない。

抗うつ薬の臨床開発

人間を対象とした医薬品の開発は、製造販売を厚生労働省によって承認されることを目指して実施されている。具体的には、表4に示した各段階の試験が、「医薬品の臨床試験の実施の基準」（厚生省令第二八号・平成九年四月一日施行、厚生労働省令第六八号・平成二一年三月三一日改正）[2]に則った治験として実施される。この省令では、研究参加者（被験者）の人権と安全性の確保、臨床データの信頼性の確保をはかり、治験が倫理的な配慮のもとに科学的で適正に実施されるための基準が示されている。なお、治験を実施する前には、治験を依頼しようとする者（製薬企業等）またはみずから治験を実施しようとする者（医師等）は、薬事法に従い、治験計画届をＰＭＤＡに提出しなければならない。

表4　抗うつ薬開発における臨床試験

1	臨床薬理試験
2	探索的試験
3	検証的試験
4	長期投与試験

抗うつ薬候補となる化学物質（治験薬）の有効性および安全性を検討するために考慮するべき、人間を対象とした最初のステップは、ＩＣＨガイドライン等の適切なガイドラインに従って実施される臨床薬理試験である。非臨床試験で得られた情報をもとに、治験薬を初めてヒトに適用する臨床薬理試験を実施する。また、臨床薬理試験は、うつ病患者ではなく、比較的限定された数の健康成人ボランティア等を対象とし、治験薬のヒトにおける安全な投与量の検討を主な目的とする。また、この段階で治験薬の薬物動態（吸収、分布、代謝、排泄）の検討も行う。健康成人を対象とするほかに、高齢者や肝機能障害または腎機能障害患者等を対象とした検討が必要な場合や、薬物相互作用の検討が必要な場合がある。

次に、初めてうつ病患者を対象に、探索的試験を実施する。探索的試験では、うつ病患者を対象として用量反応関係を明らかにする。

さらに、その後に実施される検証的試験では、探索的試験によって投与の用量が推定された治験薬について、プラセボ対照ランダム化二重盲検比較試験によってその有効性を検証し、安全性を検討する。得られた結果の臨床的意義を検討するために、プラセボおよび治験薬のほかに、現在の標準治療薬と臨床で位置づけられる抗うつ薬を対照薬群として設定する場合もある。抗うつ薬の「有効性」とは何かについての議論は他稿に譲る[3][4]。

治験から得られる結果の解釈には制約があることがよく知られている。たとえば、比較的短期間で実施される探索的試験および検証的試験では、長期における有効性および安全性を十分に検討することができない。しかし、うつ病は長期治療が一般的であるため、長期投与の有効性や安全性も検討する必要がある。また、新規抗うつ薬が承認され、販売が開始されると、治験の時のようにきわめて限定された患者集団以外にも、より広いうつ病患者群にその薬が用い

られるようになる。そのため、承認後にも、製造販売後調査や製造販売後臨床試験が実施される。治験期間中に明らかとされなかった安全性に関する貴重な情報が収集されることも少なくない。

また、抗うつ薬の治験においては、有効性および安全性評価に適した均質な集団を選択できるよう国際的に普及した診断基準を用いて選択基準を設定する必要があり、症状評価のみで規定することは避けられる。現時点での診断基準としては、米国精神医学会が作成した診断基準であるDSM-IV-TR[5]で定義される「大うつ病性障害」の使用が標準となっている。

おわりに

近年、うつ病をはじめとする精神疾患の病態理解が進んでおり、製薬企業各社は治療効果が期待される多くの新規抗うつ薬候補物質を探索している。今後、これらの化学物質の中から優れた抗うつ薬が開発され、一日も早く日常臨床において利用可能となることを期待している。

一方、適切な医薬品開発を実現するためには、新規抗うつ薬の恩恵を享受すべき患者、臨床家、医学研究者、生物統計家、治験コーディネーター（CRC）等の臨床開発スタッフ、倫理審査委員、製薬企業、規制当局等の協働が欠かせない。抗うつ薬の開発が適切に実施されることにより、うつ病の治療やケアがさらに進歩することを祈念している。

（やまだ・みつひこ／精神医学）

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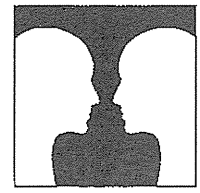

Factors affecting assessment of severity of aggressive incidents: using the Staff Observation Aggression Scale – Revised (SOAS-R) in Japan

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Accessible summary

- Consumer gender and age, and nurse gender influenced the perception of overall severity of aggressive incidents, in addition to the aggression data provided by the Staff Observation Aggression Scale – Revised (SOAS-R) scores.
- The factors influencing assessments of aggression incident severity can be identified from the severity scores provided by concurrently conducting objective (i.e. SOAS-R) and overall (i.e. visual analogue scale) assessments.

Abstract

The aim of this study is to investigate factors associated with overall judgements of aggression severity as provided by ward nurses, using the Japanese-language version of the Staff Observation Aggression Scale – Revised (SOAS-R). Nurses who observed 326 aggressive incidents involving psychiatric inpatients at five mental health facilities in Japan provided their assessments of the incident severity both on the established rating scale, the SOAS-R, and on a visual analogue scale (VAS), a one-item scale to indicate overall aggression severity. To evaluate the factors influencing the VAS severity scores, a multiple regression analysis was performed, in which consumer, nurse and ward characteristics were added consecutively, along with SOAS-R severity scores as independent variables. SOAS-R scores explained 17.6% of the VAS severity scores. Independently from the SOAS-R scores, the gender and age of the aggressive consumers (adjusted $R^2 = 10.0\%$), as well as the gender of the nurses who reported the aggression (adjusted $R^2 = 4.1\%$), each explained VAS severity score to a significant degree. Apart from the SOAS-R scores, consumer and nurse characteristics appeared to influence the overall judgements of severity of aggressive incidents, which may be connected to decisions about the use of coercive measures, such as seclusion/restraint or forced medication.

Introduction

Aggressive incidents occur frequently during inpatient treatment in psychiatric settings (Nijman *et al.* 2005). Such incidents often threaten the safety of consumers and staff and may result in the use of coercive measures such as seclusion or restraint (Fisher 1994, Busch & Shore 2000). Seclusion and restraint are widely recognized as an intervention that has negative consequence for the consumers, such as a violation of their autonomy and respect, and a traumatic experience for them (Huckshorn 2004). Staff members who witness an aggressive incident must afterwards document and evaluate the event. However, they may experience emotions such as fear, anger or shame regarding the incident (Needham *et al.* 2005), which can undermine the objectivity of their evaluation. A lack of objectivity may result in underestimation of a potential danger with consequent risks or, conversely, an exaggeration of this danger, which may prompt unnecessary initiation or prolongation of seclusion or restraint. To avoid such mistakes and improve coercion practices, it is therefore important to understand what are the elements associated with the staff's assessment of aggression severity in incidents that have resulted in seclusion or restraint.

The Staff Observation Aggression Scale – Revised (SOAS-R) was developed in order to record the nature and severity of aggressive incidents in a time-efficient manner (Nijman *et al.* 1999). The SOAS-R consists of checklist items asking whether specific aspects of aggressive behaviour occurred, and staff members have to mark the items that apply to the aggression they experienced or witnessed objectively. Therefore, by using the SOAS-R, it is possible to quickly document various aspects of aggressive incidents as well as perform post-event situation analyses on the basis of this information. For these reasons, the SOAS-R is widely applied in psychiatric wards worldwide (Nijman *et al.* 1999, 2005).

Previous studies investigating the reliability of the Staff Observation Aggression Scale (SOAS) (Palmstierna & Wistedt 1987), on which the SOAS-R is based, have been conducted in various countries (Nijman *et al.* 2005), and have demonstrated a correlation coefficient of 0.61–0.87 for reliability between individuals performing the assessments. Validity has been confirmed for both the SOAS and SOAS-R. Although an evaluation of concurrent validity for the SOAS-R based on a severity rating using the visual analogue scale (VAS) produced correlation coefficient values ranging from 0.49 to 0.62 (Nijman *et al.* 2005), high values of greater than 0.7 were not obtained.

Thus, unlike SOAS-R scores, which are calculated on the basis of the checklist items, consisting of mostly specific and observable behaviours, the addition of a VAS severity assessment provides an additional option for staff members to provide their personal opinion on the overall severity of an aggressive incident they just experienced. It is possible that certain characteristics of the reporting staff members, as well as those of the aggressive consumers, are associated with these judgements of aggression severity. The perceived severity and dangerousness of the disruptive behaviour displayed by the consumer will influence the decisions to use restrictive measures, such as seclusion or restraint (Nijman *et al.* 1999).

The aim of this study is to consider what factors influence the overall judgement made by ward nurses of the severity of aggressive incidents. To this end, the associations between consumer, nurse and ward characteristics, in addition to SOAS-R scores, are considered in relation to the VAS assessments of overall aggression severity made by the nurses.

Materials and methods

Settings

This study was conducted over an 8-month period starting in November 2008 for six wards in four hospitals and for a 2-month period starting from November 2008 for nine wards in one hospital. According to the medical reimbursement system in Japan, four wards were classified as 'emergency wards' (E type), five wards as 'acute wards' (A type) and six wards as 'wards with a nurse ratio of 15 consumers to 1 nurse' (S type). The requirements for both an emergency and acute ward are that more than 40% of the inpatients are those newly admitted, and 40% of the newly admitted consumers are to be discharged to their home within 3 months after admission. The additional requirement for an emergency ward is the responsibility to accept more involuntary admissions than other types of ward, under the order of the prefectural governor of the catchment area, which is stricter than for admissions under proxy consent. Accordingly, the average nurse allocation on an emergency ward is 10 consumers per nurse per day, compared to 13 consumers on an acute ward.

The average number of beds was 53.0 [standard deviation (SD) = 10.8]. The most frequent diagnoses were F20-F29 (schizophrenia group) of the International Classification of Disease, 10th Edition (ICD-10). The prevailing age range of subjects were adults aged 20–65 years for 13 wards and geriatric consumers aged over 65 years at two wards. Average length of hospital stay for 2007 was less than 3 months for nine wards (all E and A type wards) and was over 10 years for the remaining six wards (all S type wards).

The mean of cumulative secluded days per 1000 patient days in the E type, A type and S type wards in November 2007 was 401 (SD = 245) days, 83 (SD = 80) days and 47 (SD = 52) days, respectively, and the mean of cumulative mechanical restrained days was 41 (SD = 53) days, 10 (SD = 11) days and 1 (SD = 2) day, respectively.

Instrument

The SOAS-R is used to assess the severity of aggressive incidents which are defined as 'any verbal, non-verbal or physical behavior that was threatening (to self, others or property), or any physical behavior that did harm (to self, others or property)' (Morrison 1990). The SOAS-R scores are comprised of a distribution of scores ranging from 0 to 9 according to the severity of the checked item (Nijman *et al.* 1999, 2005), with the score for the highest checklist item in the column being the column score. The first column 'Provocation' is comprised of items with scores ranging from 0 to 2. Similarly, the second column 'Means used by the patient' contains items for which the scores can range from 0 to 3, the third column labelled 'Target of aggression' can range from 0 to 4, the fourth column labelled 'Consequence for victim' can range from 0 to 9, and the fifth column labelled 'Measures to stop aggression' can range from 0 to 4 severity points. The sum of the five column scores forms the total SOAS-R score. The theoretical range of total SOAS-R scores is from 0 to 22 points, with higher scores indicating greater incident severity.

Development of SOAS-R Japanese version

Permission for the development of a Japanese version of the SOAS-R was obtained from the first author of the SOAS-R (H. N.). The English version of the SOAS-R was translated into Japanese by two independent psychiatrists (T. N. and N. S.) skilled in English and, based on each of these, the Japanese draft was prepared through discussion with two translators, another psychiatrist, two psychiatric nurses and a psychiatric occupational therapist all together. Two native English speakers then independently performed a back-translation of the Japanese draft from Japanese to English. The first author of the SOAS-R (H. N.) verified these two back-translations, and the selection of the final Japanese-language translation was made through discussion between the authors (H. N. and T. N.).

Regarding inter-rater reliability of the Japanese-language version of the SOAS-R, of 168 incident records completed on the wards for a period of 2 months starting in November 2008, independent SOAS-R assessments were made by two nurses for 33 incidents (19.6%) when they actually saw the incident happen. It was possible to perform a complete analysis with no missing items for 26 of the incidents (78.8%), for which a significant and high correlation coefficient between the total SOAS-R severity scores was found ($n = 26$, $r = 0.701$, $P < 0.001$), which indicates that the inter-rater reliability of the severity scores as assessed with the Japanese SOAS-R is fair-to-good.

To evaluate concurrent validity, VAS severity assessments were used, in which nurses can mark on a 100-mm line the perceived severity of the aggressive incident they witnessed, ranging from 'not severe at all' at the 0-mm end to 'extremely severe' at the 100-mm end. It was possible to evaluate 290 completed SOAS-R reports that had no missing VAS severity assessments or SOAS-R rating items out of 326 reports gathered during the survey period for the wards (89%). A modest, but significant correlation coefficient ($n = 290$, $r = 0.387$, $P < 0.001$) was found between the SOAS-R severity scores and the VAS severity judgements obtained this way.

Although these findings confirmed to a certain extent the reliability and validity of the Japanese SOAS-R for rating aggressive incidents occurring on Japanese psychiatric inpatient wards, it should be noted that earlier studies found somewhat higher correlations for the concurrent validity with the VAS ratings (Nijman *et al.* 2005).

Procedures

Nurses recorded and assessed the aggressive incidents by means of the Japanese SOAS-R and the VAS severity assessments (which had also been utilized for the development of the Japanese version of the SOAS-R). In addition, nurses recorded details about the consumers who engaged in aggressive behaviour (gender, age and diagnosis), as well as details about themselves (gender, age and years of psychiatric nursing experience) during the survey period.

The study protocol was approved following an ethical review by the National Center of Neurology and Psychiatry in Japan.

Statistical analysis

Descriptive statistics were used to explore the characteristics of aggressive consumers and the nurses who rated the aggressive incidents. Then, four regression analyses were performed with VAS severity score set as the dependent variable and consumer characteristics (gender, age, diagnosis) set as the independent variables in Model 1, adding nurse characteristics (gender, years of psychiatric experience) for Model 2, adding ward characteristics (ward type) for Model 3, and finally adding SOAS-R score for Model 4. SPSS ver15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses.

Table 1
Multiple regression analysis of visual analogue scale severity scores as the dependent variable in association with consumer and nurse characteristics and Staff Observation Aggressive Scale – Revised (SOAS-R) severity scores as the independent variables

	Model 1	Model 2	Model 3	Model 4
	β	β	β	β
Consumer characteristics				
Female (ref = male)	−0.241***	−0.214**	−0.202**	−0.238***
Age	−0.169**	−0.094	−0.039	−0.135*
Diagnosis (ref = F2)				
F3	−0.173**	−0.190**	−0.181**	−0.156**
Other	−0.030	−0.010	0.007	0.005
Nurse characteristics				
Female (ref = male)		−0.193**	−0.170*	−0.176**
Years of experience as a psychiatric nurse		0.054	0.049	0.047
Ward type (ref = E ward)				
A ward			−0.149*	−0.086
S ward			−0.197*	−0.111
SOAS-R				
SOAS-R severity score				0.421***
R^2	0.114	0.162	0.187	0.361
adjR^2	0.100***	0.141***	0.160***	0.336***
ΔR^2		0.041	0.019	0.176

E ward, emergency ward; A ward, acute ward; S ward, ward type with staff ratio of 15 consumers to 1 staff.
***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

Results

Occurrence rate and severity of aggressive incidents

Three hundred and twenty-six incidents were recorded and assessed using the SOAS-R and the VAS, for a rate of 3.28 incidents per 1000 beds (1.23/bed/year). By ward type, the rate of occurrence was 3.24 (1.65/bed/year) for E type wards, 3.27 (0.96/bed/year) for A type wards and 3.35 (1.22/bed/year) for S type wards. Mean SOAS-R score was 10.7 (SD = 4.7) and mean VAS severity score was 52.8 (SD = 26.2).

Consumer and nurse characteristics

Of consumers who participated in aggressive incidents recorded with the SOAS-R, 64.7% were male, mean age was 50.1 (SD = 17.7, range 17–88) years, and the primary ICD-10 diagnoses were F20-F29 (schizophrenia group, 65.4%), F30-F39 (mood disorders, 13.4%), F10-F19 (disorders due to psychoactive substance use, 7.2%) and F00-F09 (organic, including symptomatic, mental disorders, 4.8%). Of nurses who provided SOAS-R ratings, 45.5% were male, the mean age was 34.0 years (SD = 8.7, range 21–60), and the mean psychiatric nursing experience was 9.3 years (SD = 7.8, range 0–36).

Contribution to VAS severity scores

The explanatory value of consumer characteristics for Model 1 was 10.0%. For the other models, the explanatory value was 4.1% for nurse characteristics, 1.9% for ward characteristics and 17.6% for SOAS-R score. In Model 4, VAS severity score was explained to a significant degree by consumer gender and age, and nurse gender, with male consumer and nurse gender and younger consumer age corresponding to higher VAS scores (Table 1). By diagnoses, the VAS severity score was significantly lower for the F30-F39 group than that for the F20-F29 group. No correlations exceeded 0.45 for correlation matrices between variables.

Discussion

The regression analyses revealed that SOAS-R scores explained 17.6% of the VAS severity scores, while consumer gender and age (adjusted R^2 = 10.0%), and nurse gender (adjusted R^2 = 4.1%) were significant explanatory factors for VAS severity score.

In this study, although a significant relationship was found between the SOAS-R and the VAS severity scores, the observed correlation coefficient of 0.387 was lower than that seen in previous studies (0.49–0.62) (Nijman *et al.* 2005). In other words, the correlation between the VAS severity assessments, which probably include more subjective elements, and the SOAS-R scores, which are primarily comprised of more objectively rated items, was modest. The results of regression analyses suggest that adding elements related to consumer or nurse characteristics to SOAS-R score increased the correlation with the overall judgement of severity of aggressive incidents. Even if the SOAS-R check items are the same, if the consumer is

a younger man, or if the rating nurse is a man, these overall judgements have a tendency to be more severe.

This finding may not be surprising in the light of common sense and face validity of the VAS. However, to the best of the authors' knowledge, the observed phenomenon has not been previously explored with an appropriate scientific methodology.

Aggressive incidents frequently lead to seclusion or restraint, and younger consumers are also found to be subjected to seclusion or restraint more frequently (Gudjonsson *et al.* 2004, Migon *et al.* 2008, Keski-Valkama *et al.* 2010). Likewise, some studies suggest that male consumers are more frequently subjected to seclusion (Gudjonsson *et al.* 2004), although others find no gender difference in this respect (Keski-Valkama *et al.* 2010). While one can imagine that young male consumers might be more likely to behave aggressively, it cannot be ruled out that such consumer characteristics also could lead to an overestimation of dangerousness and a higher subjective perception of severity. Of course, this may have to do with the potential consequences in case of further escalation. These consequences may be more severe in cases where the aggressor is a young man compared to an older woman.

However, a previous report revealed a larger number of violent female consumers than violent male consumers (Weizmann-Henelius & Suutala 2000), and results from other reports indicated that mental health professionals were particularly limited in their ability to assess the risk of future violence for female consumers (Skeem *et al.* 2005). Therefore, the risk of underestimation in regard to female aggressive incidents requires attention.

One could argue that male nurses might be psychologically and physically more prepared to face violence and thus should be less cautious of the potential risks of underestimation of aggression and hence of the risks of earlier discontinuation of seclusion/restraint. In some studies, nurses and physicians appeared to rely heavily on workforce, especially on male nurses, in aggressive situations in order to avoid seclusion or restraint (Kontio *et al.* 2010). Interestingly, our results showed quite the opposite, as male nurses in general tended to assign higher VAS severity scores than female nurses. Correlations with gender and perception of aggression, such as whether it was functional (communicative and protective for the consumer) or dysfunctional (offensive, destructive or intrusive aspect of feeling victimized), were explored in earlier studies using the Perception of Aggression Scale (Needham *et al.* 2004, Palmstierna & Barredal 2006). However, the results were inconsistent. In the present study, it may be difficult to speculate how gender alone played a role in judging the severity of aggressive behaviour.

As far as we know, this study is one of the first to investigate both consumer and nurse characteristics in association with the severity of aggressive behaviour as perceived by the rating staff member. The variables included in this study, however, were rather global and crude. This analysis method, when psychological factors are included as independent variables, will clarify to which extent those factors influence the assessment of the severity of aggressive behaviour.

According to a recent report by Bowers *et al.* (2011), the better functioning wards, in which the staff have positive attitudes to difficult consumers and feel lower burnout, and which were assessed to have good leadership and teamwork by ward staff, seemed to have significantly lower rates of containment. Therefore, staff perception of their own characteristics and their wards environments may be associated with a high psychological impact of aggressive incidents. We believe a follow-up study is worthwhile to investigate these aspects in more detail.

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Declaration of interests

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RESEARCH ARTICLE Open Access

Is antipsychotic polypharmacy associated with metabolic syndrome even after adjustment for lifestyle effects?: a cross-sectional study

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Abstract

Background: Although the validity and safety of antipsychotic polypharmacy remains unclear, it is commonplace in the treatment of schizophrenia. This study aimed to investigate the degree that antipsychotic polypharmacy contributed to metabolic syndrome in outpatients with schizophrenia, after adjustment for the effects of lifestyle.

Methods: A cross-sectional survey was carried out between April 2007 and October 2007 at Yamanashi Prefectural KITA hospital in Japan. 334 patients consented to this cross-sectional study. We measured the components consisting metabolic syndrome, and interviewed the participants about their lifestyle. We classified metabolic syndrome into four groups according to the severity of metabolic disturbance: the metabolic syndrome; the pre-metabolic syndrome; the visceral fat obesity; and the normal group. We used multinomial logistic regression models to assess the association of metabolic syndrome with antipsychotic polypharmacy, adjusting for lifestyle.

Results: Seventy-four (22.2%) patients were in the metabolic syndrome group, 61 (18.3%) patients were in the pre-metabolic syndrome group, and 41 (12.3%) patients were in visceral fat obesity group. Antipsychotic polypharmacy was present in 167 (50.0%) patients. In multinomial logistic regression analyses, antipsychotic polypharmacy was significantly associated with the pre-metabolic syndrome group (adjusted odds ratio [AOR], 2.348; 95% confidence interval [CI], 1.181-4.668), but not with the metabolic syndrome group (AOR, 1.269; 95%CI, 0.679-2.371).

Conclusions: These results suggest that antipsychotic polypharmacy, compared with monotherapy, may be independently associated with an increased risk of having pre-metabolic syndrome, even after adjusting for patients' lifestyle characteristics. As metabolic syndrome is associated with an increased risk of cardiovascular mortality, further studies are needed to clarify the validity and safety of antipsychotic polypharmacy.

Background

Metabolic syndrome is a cluster of metabolic dysfunctions, including central obesity, hypertension, glucose, and lipid abnormalities. Those with the syndrome have a two- to threefold increase in cardiovascular mortality and a two-fold increase in all-cause mortality [1]. Patients with schizophrenia are more likely to have metabolic syndrome than the general population [2].

To date, a few research studies have reported an association between antipsychotic polypharmacy and metabolic syndrome [3,4]. Limited evidence currently exists regarding the benefits of antipsychotic polypharmacy, and antipsychotic monotherapy is consistently recommended in the treatment of patients with schizophrenia [5,6]. Antipsychotic polypharmacy is, however, commonplace in the treatment of schizophrenia [7-11], and has been reported to occur in a wide range (13-90%) of cases. In Japan, in particular, polypharmacy has been reported to occur at a higher rate than in other countries [12].

If antipsychotic polypharmacy, which is not recommended, is associated with a greater risk of metabolic syndrome, the spread of polypharmacy is a serious concern. However, it remains unclear among earlier studies

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whether antipsychotic polypharmacy is associated with metabolic syndrome as a direct result of patients' unhealthy lifestyle. Patients with schizophrenia are likely to make poor dietary choices, have low rates of physical activity, and smoke cigarettes [13], and their unhealthy lifestyle is assumed to be associated with an increased risk of metabolic syndrome. However, as little information is available on the association between metabolic syndrome and antipsychotic polypharmacy in conjunction with patients' lifestyle, further research is needed any such association.

In this cross-sectional study, we aimed to investigate the relationships between antipsychotic polypharmacy and metabolic syndrome in outpatients with schizophrenia, with adjustment for the effects of lifestyle.

Methods

Study participants

Participants who lived in the community and received psychiatric outpatient treatment were recruited from April 2007 to October 2007. The study inclusion criteria were: regular attendance at Yamanashi Prefectural KITA Hospital, Japan; an ICD-10 diagnosis of schizophrenia, schizotypal and delusional disorders; and age 18 years or older.

During the study period, of all 599 patients who fulfilled the inclusion criteria in this study, 399 consented to participate in the study. As 65 of these patients did not complete the questionnaire, data from 334 patients were used in the analysis.

The study design was approved by the Ethics Committees of Yamanashi Prefectural KITA Hospital. Written informed consent was obtained from all participants.

Assessment

Assessment in this study consisted of sociodemographics (age, gender), duration of psychiatric treatment, family history of lifestyle-related disease, metabolic syndrome, prescribed antipsychotics, and participants' lifestyle. In addition, psychiatrists in charge of the participants assessed the patients on the Global Assessment of Functioning (GAF) scale.

Metabolic syndrome

Rather than using the discrete diagnostic category of metabolic syndrome, we divided metabolic syndrome into four groups based on severity of metabolic disturbance (metabolic syndrome, pre-metabolic syndrome, visceral fat obesity and normal), since metabolic syndrome is continuously disturbed in nature [14]. In accordance with the diagnostic criteria proposed by the Japanese Committee of the Metabolic Syndrome Diagnostic Criteria [15], metabolic syndrome was defined as visceral fat obesity (abdominal circumference: ≥85 cm for males, ≥90 cm for females) and at least two of the following three criteria: elevated blood glucose (fasting glucose level ≥110 mg/dL), lipid abnormalities (triglycerides ≥150 mg/dL and/or high-density lipoprotein (HDL) cholesterol <40 mg/dL), and elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg). Current treatment with diabetes, lipid-lowering, or antihypertensive medication fulfilled the criterion for elevated blood glucose, lipid abnormality, and elevated blood pressure, respectively. Pre-metabolic syndrome was defined as the presence of one of the above three criteria in addition to visceral fat obesity.

We classified metabolic syndrome in the following four groups: the normal group did not fulfill the criteria of visceral fat obesity, the visceral fat obesity group fulfilled only the criteria of visceral fat obesity, the pre-metabolic syndrome group was defined by the presence of only one of the three criteria above in addition to visceral fat obesity, and the metabolic syndrome group was defined by the presence of at least two of the three criteria above in addition to visceral fat obesity. Participants were given written instructions to fast overnight on the day before assessment, and asked to confirm their fasting status before blood samples were taken. A single venous blood sample was withdrawn and analyzed for glucose, triglycerides, and HDL cholesterol. Nurses measured abdominal circumference and blood pressure.

Prescribed antipsychotics

We investigated prescribed antipsychotics from patient charts on the day we measured the participant's metabolic syndrome parameters. All dosages of antipsychotic drugs were converted into chlorpromazine equivalents [16] in order to estimate the total daily chlorpromazine-equivalent dose.

In this study, polypharmacy was defined as the concomitant use of two or more antipsychotics, while monotherapy was defined as the use of only one antipsychotic.

Antipsychotic treatment in Japan was subject to special conditions during the study period. First, clozapine had not been launched at this time. Second, olanzapine and quetiapine were contraindicated for patients with diabetes or a history of diabetes because it was reported that some patients that were treated with olanzapine and quetiapine developed severe hyperglycemia and diabetic coma.

Assessment of participants' lifestyle

We assessed the participants' dietary habits, physical activity, and smoking habits. With regards to dietary habits, these were assessed by an originally designed self-reporting questionnaire that consisted of the following four items, which have been used in earlier studies: snack eating (Do you eat snacks?), intake of fatty foods (Do you