

White Paper

Uncovering Insights: Tapping into APAC's Potential for Obesity Clinical Trials

A Survey Across Ten Asia Pacific Countries

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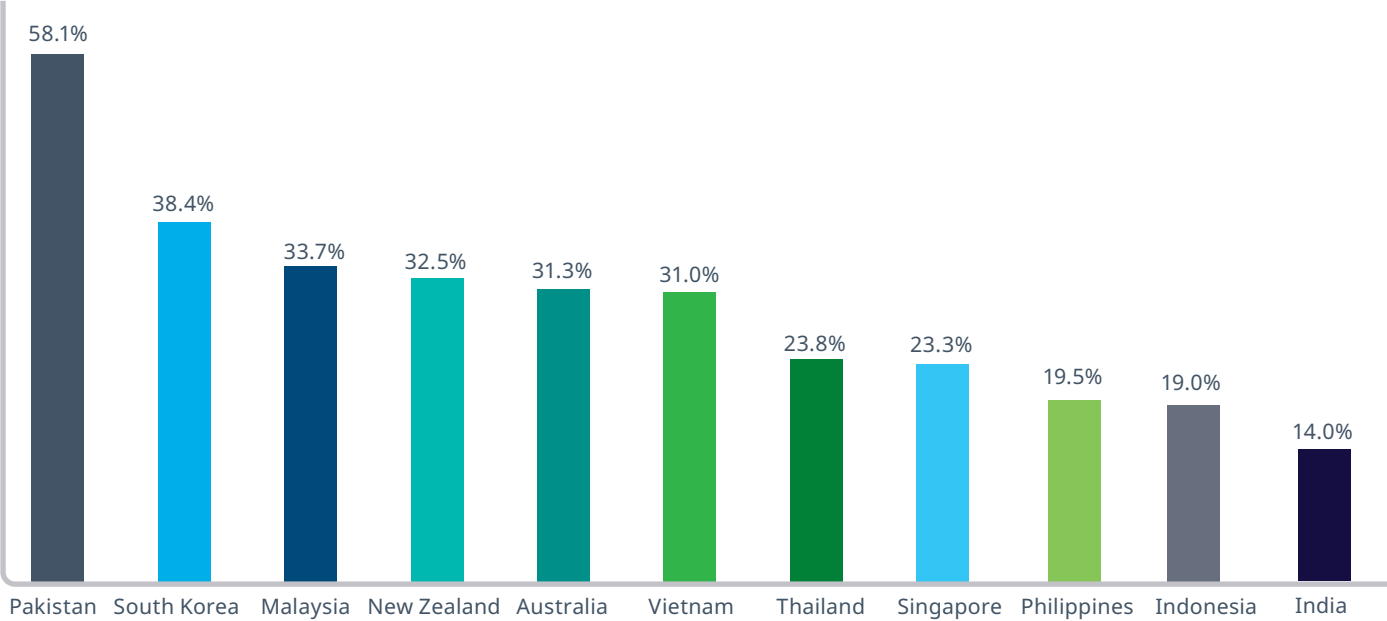
Introduction

Obesity has become a global health problem. The global prevalence of obesity, defined as a body mass index (BMI) $\geq 25\text{kg/m}^2$, is predicted to rise from 14% to 24% in 2020 and 2035, respectively. It is estimated that almost 2 billion will be affected by 2035.¹

In the Asia Pacific (APAC) region, obesity has also become a major public health concern with increasing prevalence rates. Australia has a high obesity prevalence of 31.3% based on an Australian National Health Survey in 2017–18.² It is similar in New Zealand at 32.5%.³ In India, the prevalence of obesity is approximately 14% using a BMI cut-off for the Asian population ($\geq 27.5\text{ kg/m}^2$).⁴ In South Korea, the overall prevalence of obesity (BMI $\geq 25\text{ kg/m}^2$) increased from 30.2% in 2012 to 38.4% in 2021, a 1.27-fold increase in 9 years.⁵ In Pakistan, World Health Organization (WHO) data indicates that 43.9% of the population is obese, and when Asian BMI cutoffs are applied, the prevalence is higher at 58.1%.⁶

Among countries in Southeast Asia, Malaysia has the highest obesity prevalence rate of 33.7% using a BMI cut-off of $\geq 27.5\text{ kg/m}^2$ and 19.7% with BMI of $\geq 30\text{ kg/m}^2$.⁷ In Indonesia, the prevalence of obesity among all adults is 19.0% using the national obesity cut-off of BMI $\geq 27\text{ kg/m}^2$.⁸ In Thailand, approximately 19.0% were classified as class I obesity (BMI 25.0–29.9 kg/m^2), and 4.8% as class II obesity (BMI $\geq 30.0\text{ kg/m}^2$).⁹ There was an increase in the prevalence of obesity in Vietnam from 10% in 2009 to 15% (male) and 16% (female) in 2015 based on a BMI $\geq 25\text{ kg/m}^2$.¹⁰ In the Philippines, the obesity prevalence in 2021 was 12.2% among females and 7.3% among males with BMI cutoff of $>30\text{kg/m}^2$.¹¹ It is the opposite in Singapore wherein the prevalence of obesity was more common among males (13.1%) than females (10.2%) based on a National Population Health Survey in 2022 (Figure #1).¹²

Figure 1: Prevalence of obesity in APAC



Global status of obesity trials

Clinical practice guidelines recommend the use of pharmacologic treatments together with lifestyle interventions to manage obesity. However, previously available treatments for obesity often produce underwhelming results, leading to a demand for new and more effective drugs. New knowledge on the body's weight regulation mechanisms and the role of the gut-brain axis on controlling appetite has led to the discovery and development of safer and effective obesity treatments, mostly hormone-based like glucagon-like peptide -1 (GLP-1) receptor agonists, many of which are already undergoing phase III trial testing. Additionally, agents with different entero-pancreatic hormone mechanisms of action are in the early-phase clinical trials.¹³

The obesity treatment space is booming with 80+ active players, including key obesity companies like Pfizer, Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Shionogi Regor Pharmaceuticals, and others working to develop 100+ pipeline therapies for obesity treatment.¹⁴ As of August 2024, IQVIA's Pipeline and Trial Link listed a total of 106 clinical programs in development for 84 drugs with different mechanisms of action. There are currently 36 phase III trials for 13 drugs, 24 phase II trials for 29 drugs, and 46 phase I trials for 42 drugs. In addition, 23 products are in the pre-clinical phase, and 6 more in discovery. The pipeline is dominated by GLP-1 receptor agonists followed by agents that target calcitonin receptor (CALCR), dual agonists of glucose -dependent insulinotropic peptide (GIP) receptor and GLP-1 receptor, and melanocortin-receptor. Many of the drugs in development are small molecules and peptides.¹⁵

Despite the large number of obesity trials occurring worldwide, the proportion of trial participants in Asia is very low. Only 1.4% of obesity trials listed enrollment from any of the APAC countries.¹⁶

Objectives

Our aim was to collect information on the epidemiology and demographics, diagnosis, and local standard of care of obese and overweight patients in the Asia Pacific region (APAC), and to analyze and interpret similarities and differences across the different APAC countries and the rest of the world. The data and its analysis were intended to evaluate the potential of APAC investigative sites and Investigator credentials and experience for the conduct of obesity clinical trials in the region.

Real-time data available from APAC centers through a systematically executed site feasibility survey has been presented and evaluated in the light of anticipated challenges and favorability for conducting obesity trials in APAC region.

Methodology

An on-line cross-sectional survey was conducted from 18 Oct 2024 to 20 Nov 2024 to collect data from potential investigative centers across 10 countries in APAC.



A detailed questionnaire was created by the project team addressing the collection of required information. IQVIA database and the public database were hand-searched for clinical centres (sites) and investigators (medical practitioners conducting clinical trials) related to metabolic disease studies.

The questionnaire was designed to ensure collection of data related to the epidemiology of obesity disease across APAC, patient pathways, standard practice of diagnosis, management, and treatment of obesity at these centers, and the clinical trial experience of potential investigators. The survey consisted of 22 questions in toto.

EPIDEMIOLOGY (3 QUESTIONS)

- Number of newly diagnosed obese and overweight patients seen at the clinic.
- Most common comorbid conditions seen in these obese and overweight patients.

PATIENT PATHWAY (2 QUESTIONS)

- Most common specialties sending patient referrals for obesity management.

DIAGNOSIS (3 QUESTIONS)

- Tools and parameters used in evaluating obese and overweight patients.
- BMI and severity criteria classifications used to diagnose and monitor obese and overweight patients.

MANAGEMENT AND TREATMENT (10 QUESTIONS)

- Criteria for initiation of anti-obesity therapy and follow ups.
- Data on patients receiving lifestyle modification treatment and alternative therapies.
- Data on patients receiving pharmacologic agents to manage obesity.
- Approved and available prescription drugs for obesity management, complications and adverse effects seen, patient concerns regarding anti-obesity drugs.
- Data on patients who underwent bariatric surgical intervention and reasons for bariatric surgery.

CLINICAL TRIAL EXPERIENCE (4 QUESTIONS)

- Obesity clinical trial experience and interest of Key opinion leaders and investigators in participating in obesity clinical trials.

From the database, multiple clinical trial sites were identified in 11 Asian countries, namely Australia, India, Indonesia, Malaysia, New Zealand, Pakistan, Philippines, Singapore, South Korea, Thailand, and Vietnam, and outreach was performed. A total of 171 sites were contacted for the questionnaire with a target of at least 5 responses per country.

Results

A total of 138 completed questionnaires were received by the team, (81% response rate). Completed questionnaires were reviewed and verified for completeness by the project team from IQVIA. The collated datasheet was re-verified by the data analytics team, and data analysis summary was presented. A pre-specified set of descriptive analysis was performed and summary tables, listings, and graphs or charts, as relevant, were generated in discussion with project management, medical expert and medical writing team. Relevant outputs from the analyzed datasets are presented for the purpose of this report.

Investigator credentials and experience

The survey was completed in 138 sites in 10 APAC countries, namely, Australia, India, Indonesia, Malaysia, New Zealand, Pakistan, Philippines, South Korea, Thailand, and Vietnam. No response was obtained from the sites contacted in Singapore. Majority (55%) of investigators were private sector workers, followed by both private and public sector (22%) and only public sector (18%). Few worked in other healthcare sectors such as private multispecialty hospital, charitable trust, research site at public hospital and university hospital.

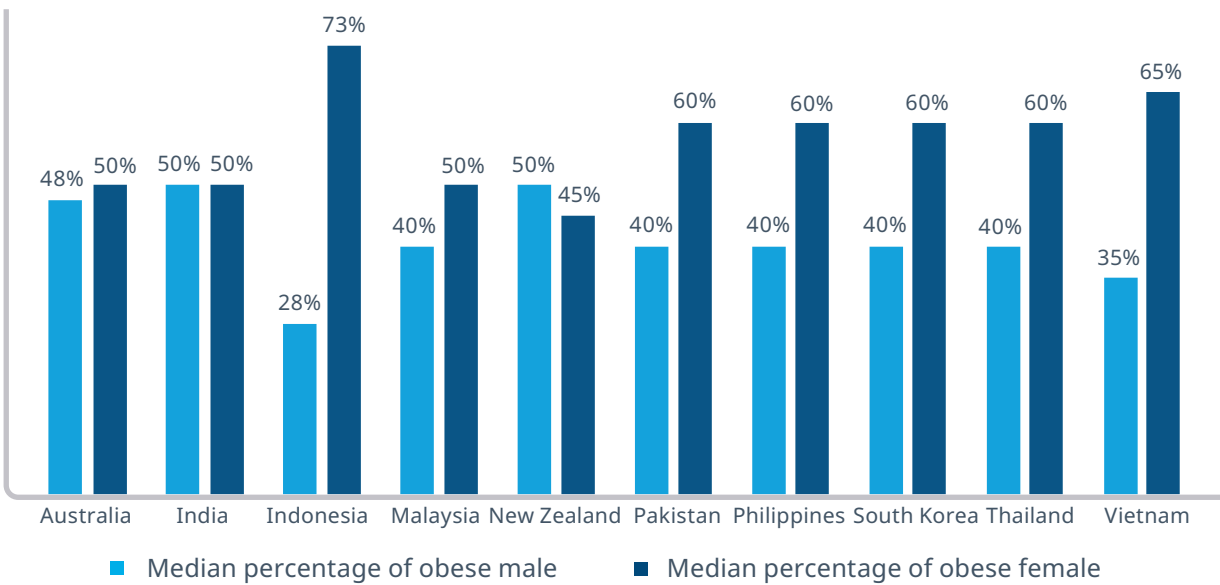
The investigators were well experienced in the therapeutic area. About 70% of the Investigators had more than 10 years of experience. On review of the specialties of the participating investigators, the top specialties included general practitioners, endocrinologists, followed by internal medicine specialists and cardiologists. Other participating investigators included clinical research consultants, family physicians, metabolic disorder specialists, gastroenterology, rheumatology, infectious disease.

Epidemiology

It was noted that majority of the patients newly diagnosed as obese were adult patients compared to adolescent/pediatric patients. This could also be attributed to the fact that pediatric specialty has not been included in the survey.

Overall, it was noted that approximately 60-70% of the obese and overweight patients are female patients with the exception of India, Australia, and New Zealand where the proportion of male and female patients was almost equal (Figure #2). The most common comorbidities in these obese and overweight patients were noted as diabetes mellitus, hypertension and dyslipidaemia. Other common comorbid conditions included obstructive sleep apnoea, heart failure, osteoarthritis.

Figure 2: Gender prevalence of obesity

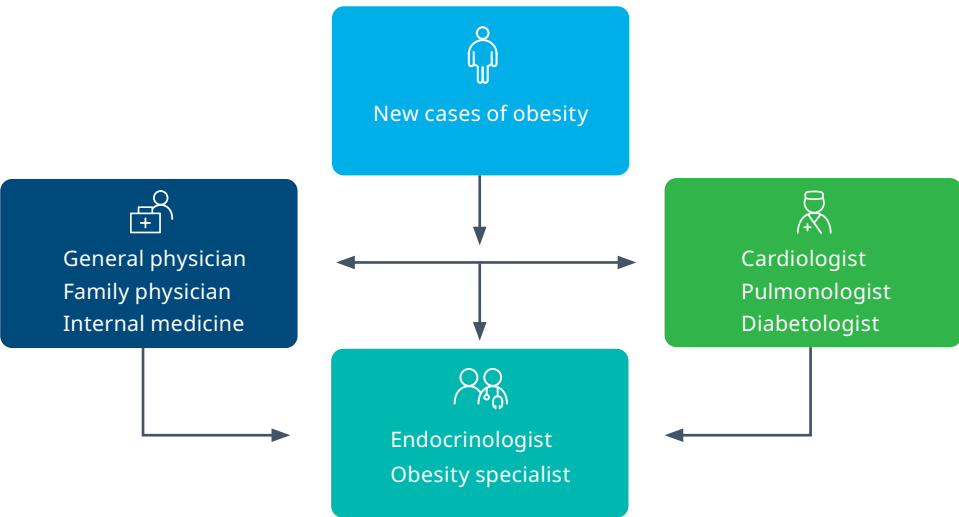


Patient pathway

Almost 70% of patients walk-in directly for consultation to their general practitioner or family physician. About 30% of patients are referred to the specialist. The most common referrals come from general practitioners (GPs), family physician, cardiologist, and pulmonologist (Figure #3).

Figure 3: Patient pathway for obesity referral in APAC

Patients would choose the physician path as per many factors, e.g.: comorbid conditions, health coverage, local practices etc.

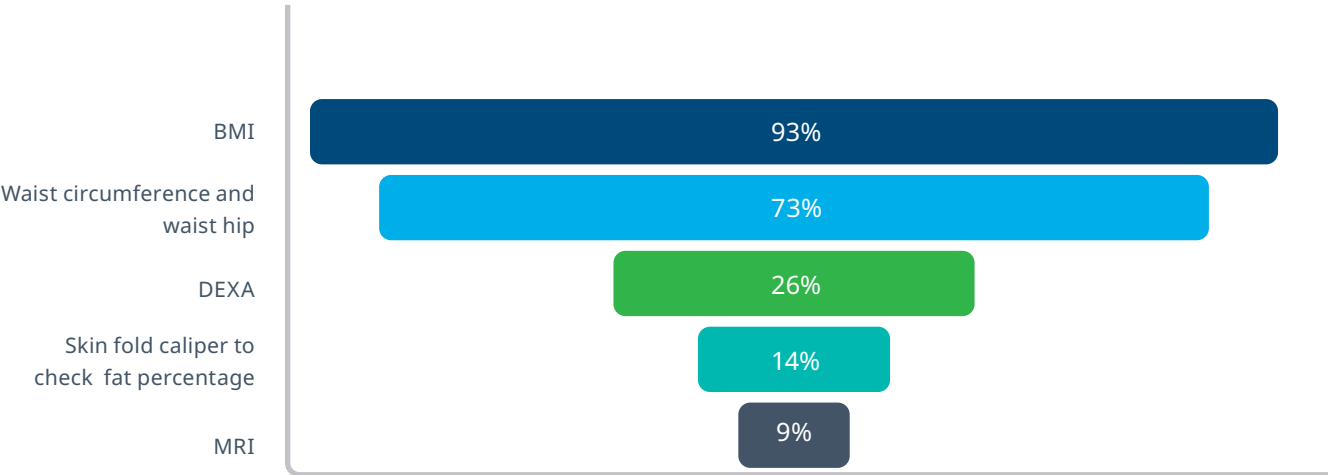


Diagnosis

METHODS TO EVALUATE OVERWEIGHT AND OBESITY

The most common method used by sites to evaluate overweight and obese patients is Body Mass Index (BMI) used by 93% of sites (n=128). This was closely followed by Waist-Circumference (WC) and waist-hip ratio measurements by 73% of sites (n=101). Dual-energy x-ray absorptiometry (DEXA) was utilized by approximately a quarter of the sites (26% n= 36) while a fewer number of sites indicated the use of skin-fold caliper and MRI at 14% and 9%, respectively. (Figure #4).

Figure 4: Tools and parameters most commonly used



Other tools used include body composition analyzer, fat measurement CT and bioelectrical impedance measurement which have been utilized by 12 sites (8%) across Australia and New Zealand, India, Indonesia, Malaysia, Pakistan, Philippines, South Korea, and Vietnam.

BMI CUTOFFS AND SEVERITY STAGING CRITERIA

Sites from Australia, New Zealand and India had higher BMI cutoffs for overweight and obesity compared to the rest of the APAC countries. Average cutoffs for overweight ranged from 25-26 kg/m² (median: 25 kg/m²), while the average cutoff range for obesity was 30-31 kg/m² (median: 30 kg/m²). The rest of the sites from Indonesia, Malaysia, Pakistan, Philippines, South Korea, and Vietnam utilized the Asian BMI cutoffs of ≥ 23 kg/m² for overweight and ≥ 25 kg/m² for obesity.

For Thailand sites, however, there were only 2 site responses with a big difference between BMI values. For overweight, the range of responses was 24-60 kg/m² (median: 42 kg/m²), and for obesity, the range was 25-40 kg/m² (median 32 kg/m²). The range for obesity BMI cutoff spanned the range of Asian BMI at the lower end and Western cutoff at the higher end.

For severity staging criteria, the American Association of Clinical Endocrinologists (AACE) guideline was most used by sites for screening and monitoring obesity with 47% (n=65) of sites utilizing it, followed by the Edmonton Obesity Staging System (EOSS) used by 28% (n=39) of sites. Other sites used the Kings Obesity Staging Criteria (KOSC), and the Cardiometabolic Disease Staging (CMDS) system.



Management and treatment

LIFESTYLE MODIFICATION AND USE OF ALTERNATIVE TREATMENTS

In South Korea and Vietnam, all patients (100%) had lifestyle modification as part of their obesity /overweight management. While for the rest of the countries, majority of their patients (~52-83%) were on lifestyle modification with no significant difference between males and females.

Only a small percentage of individuals used alternative therapies such as herbal medications as part of obesity management. The highest was noted in the Philippines and Indonesia, noted more commonly among women than men. This was followed by India and Malaysia with no significant difference between males and females, while more than twice more prevalent among women than men in Vietnam. It was least common in Australia, New Zealand, South Korea. There was no response from Thailand.

In Australia, New Zealand, South Korea and Vietnam, majority of the patients (average of 82%) were willing to discontinue their alternative therapies. While for the other countries such as India, Indonesia, Malaysia, Pakistan and Philippines, only an average of 60% were willing to discontinue these therapies.

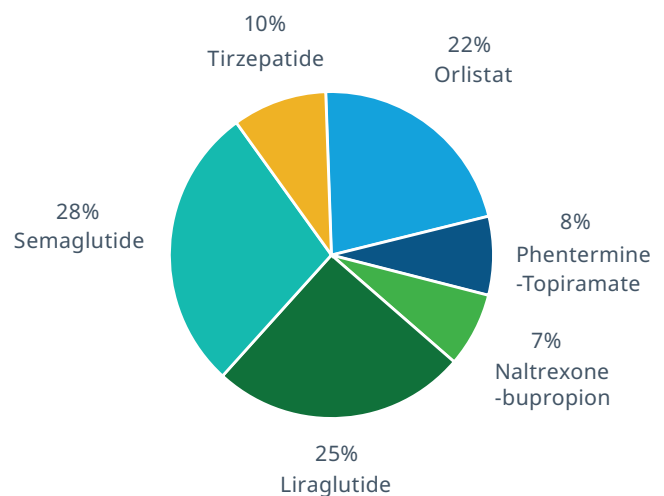
BMI CUTOFFS FOR INITIATION OF ANTI-OBESITY DRUG THERAPY

The BMI cut-off value used as basis for initiating anti-obesity drug therapy was higher in Australia, India, Pakistan, and New Zealand (average of 26-27 kg/m² in overweight individuals and 30 kg/m² in obese individuals). In Thailand, they also used a higher BMI cutoff value of 30 kg/m² for obese, however, there was no response given for overweight patients. The average BMI cut-off was lower in Indonesia, Malaysia, Philippines, South Korea, and Vietnam (average of 24 kg/m² in overweight individuals and 26 kg/m² in obese individuals).

COMMONLY PRESCRIBED ANTI-OBESITY DRUGS

The most common anti-obesity drugs used were semaglutide 28% and liraglutide at 25% followed by orlistat with 22%. To a lesser extent, other medications used were tirzepatide, phentermine-topiramate and naltrexone-bupropion (Figure #5).

Figure 5: Overall drug usage in APAC countries



Semaglutide was the most common anti-obesity drug used in Australia, India, Indonesia, Malaysia, Pakistan and Philippines. Phentermine-topiramate was the most common in New Zealand, with liraglutide in South Korea and Vietnam. In Thailand, only a minority used anti-obesity medications, namely, liraglutide (5%) and phentermine-topiramate (3%), while there was no response provided for the other medications.

All 6 medications are approved in Australia, India, Malaysia, New Zealand, Pakistan, Philippines and South Korea. In Indonesia and Vietnam, only orlistat, semaglutide and liraglutide are approved. While in Thailand, phentermine-topiramate, semaglutide and liraglutide are approved.

All 6 drugs are reimbursed in Malaysia. In Australia, orlistat, semaglutide and liraglutide are reimbursed. In India, in addition to these 3 drugs, tirzepatide is also reimbursed. In Thailand, only liraglutide is reimbursed. For the rest of the countries, they did not provide an answer regarding reimbursement status and this question was left blank.

Other medications prescribed were phentermine, diethylpropione, and anti-diabetic medications such as metformin, dulaglutide and SGLT-2 inhibitors.

OVERWEIGHT AND OBESE PATIENTS WHO ACHIEVED $\geq 5\%$ WEIGHT LOSS ON ANTI-OBESITY DRUG TREATMENT

Majority of the countries achieved the target weight loss goal of $\geq 5\%$ in only around 50% of their patients. Only Indonesia and South Korea had a higher success rate reaching up to 80-89%.

COMMON SIDE EFFECTS EXPERIENCED BY PATIENTS TAKING ANTI-OBESITY DRUGS

The common side effects that patients experienced when taking anti-obesity drugs were related to the kind of drug being taken. The most common adverse events (AEs) experienced with orlistat were diarrhea, steatorrhea, gastrointestinal issues such as nausea and vomiting, fecal incontinence, and headache. Patients taking phentermine-topiramate experienced insomnia, depression, with a lesser incidence of nausea, vomiting, dizziness, tachycardia, and constipation. With naltrexone-bupropion, patients also complained of nausea, vomiting, headache, insomnia, depression, dizziness, and gastrointestinal issues. Majority of patients taking liraglutide, semaglutide and tirzepatide experienced gastrointestinal symptoms like nausea, vomiting, fecal incontinence, diarrhea, or constipation. Patients taking semaglutide experienced more nausea, vomiting, and fecal incontinence compared to tirzepatide.

PATIENTS' CONCERNS WITH ANTI-OBESITY DRUGS

The survey showed that almost half of the respondents stated that the most common patient concern on using anti-obesity drugs is the cost of the treatment (46%), followed by adverse events/side effects (33%) and availability (21%). Other concerns included route of medication (injection), insurance coverage, lack of efficacy and long-term consequences.

PATIENTS WHO HAVE UNDERGONE BARIATRIC SURGERY

The average percentage of patients who have undergone bariatric surgery in many APAC countries was below 10% ranging between 2-8% for Vietnam (1.5%), South Korea (2.4%), Indonesia (3%), Philippines (3.16%), Thailand (5.33%), Malaysia (7.2%), and Pakistan (7.5%). It was between 10-14% in Australia (10.64%) and India (13.72%).

The most common reason for a referral for bariatric surgery was morbid obesity with 75% of sites (n=104) citing this reason. Obesity-related complications (64%, n=88) and failure of medical obesity treatment (63%, n=87) were the second and third most common reasons, and the 4th reason was patient preference (53%, n=74).



FOLLOW-UP VISITS

The frequency of follow-up visits recommended by the sites to their patients varied but the most common was monthly (31%, n=43,) followed by every 3 months (25%, n=35) follow-up. A few sites in Australia and New Zealand mentioned every 6 months and one site in Australia recommended yearly follow-up.

Clinical trial experience of participating investigators

All the investigators were interested in participating in clinical trials. All the investigators had experience of conducting at least one clinical trial. Around 12% of investigators had experience in conducting more than 4 clinical trials.

Though investigators have indicated a good pool of patients available at their site, the top barriers mentioned for recruitment in the clinical trials were stringent inclusion and exclusion criteria, too many frequencies of visits and concern over adverse events. The other potential barriers to recruitment were accessibility of the site, frequent lab and imaging requirements, concern over efficacy, investigators' concern about compliance to medication, financial issues, and lack of motivation. Once a patient is enrolled in the study, they usually complete the study and the average patients lost to follow up was estimated to be around 5%.

Overall, all the Investigators were well experienced, had the right infrastructure and patient pool to participate in clinical trials.

Discussion

In a survey reviewed by Awasthi et al,¹⁷ it was noted that the prevalence of overweight /obese population in adults and children 0–5 years of age ranged from 22.4 to 52.4%, and 1.3–7.6%, respectively. There was a higher prevalence seen in women, urban population, and higher socioeconomic status.^{18,19} Prasad et al²⁰ also reported a higher age-adjusted central obesity (48%) in females and more than two-fold increased odds of central obesity. It is known as well that

excess body fat increases the risk of death and major comorbidities such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, osteoarthritis of the knee, sleep apnea, and some cancers.^{21,22} This was reflected in the survey results of the most common comorbidities seen in overweight and obese patients.

The most common method for evaluating obesity remains the BMI and it has been established as the primary clinical tool for defining obesity.²³ However, BMI is limited as it cannot account for body composition, sex, ethnicity, and age-related adiposity.^{23,24} Furthermore, it is a poor surrogate marker for actual body fat, which is associated with detrimental health outcomes. Waist circumference (WC) is a better measure of adipose tissue as it is a good representation of visceral fat and central obesity, and combining both measurements may give a more accurate picture of a person's obesity-related complication risk.^{24,25} Clinical practice guidelines from APAC countries have recommended the use of BMI together with WC measurement to evaluate for overweight and obesity including assessment of abdominal obesity.²⁶⁻³³ Newer and more reliable methods of measuring % body fat have gained traction using emerging technologies such as multi-frequency bioelectrical impedance (MF-BIA) and DEXA, allowing for a more effective personalized obesity management.²⁵ These modalities are frequently used in obesity clinical trials, and APAC sites using these modalities as part of their standard of care may be able to easily meet procedure requirements for obesity clinical trials.

Australia and New Zealand Clinical Practice Guidelines are based on BMI and WC, as well as presence and severity of obesity-related complications. A BMI of 25.0-29.9 kg/m² is considered overweight, while a BMI of ≥30.0 kg/m² signifies obesity.^{26,27} These cutoffs are in line with the World Health Organization (WHO) BMI cutoff guidelines for overweight and obesity.²⁸ On the other hand, South Korea, Indonesia, Malaysia, Philippines, Thailand, Vietnam, India and Pakistan have adopted lower BMI cutoffs for overweight (≥23 kg/m²) and obesity (≥25 or ≥27kg/m²) compared to

Western guidelines (Table #1). Asians typically have BMIs that are 2-3 kg/m² lower than Caucasians for the same body fat percentage, therefore, there is a higher cardiometabolic risk seen in Asian populations even at BMI values that only have low or moderate risk in their Caucasian counterparts.²⁹⁻³⁴ It is interesting to note that though the clinical practice guideline for India recommends BMI cutoffs of ≥ 23 kg/m² and ≥ 25 kg/m² for overweight and obesity,³¹ respectively, survey respondents from Indian sites have listed higher values similar to Western cutoffs. This may indicate that adoption of these clinical practice guidelines to real world practice may take more time.

Obesity clinical trials generally follow WHO cutoffs for overweight and obesity. With the inclusion of APAC countries with lower BMI cutoffs, there may be a negative impact on trial recruitment as there is a subset of overweight and obese patients who are likely to be excluded because their BMI values are below the protocol requirements. This issue may be addressed by selection of big primary care and specialty weight loss and obesity centers with a large patient pool. Country or region-specific protocols that are aligned with local and regional guidelines can be developed as well.

Due to shortcomings from the use of BMI, clinical staging criteria have also been devised to determine obesity-related complication risk and are an essential component of clinical evaluation.²³ These staging criteria provide a framework wherein obesity is evaluated as a chronic disease and staged for severity. With these criteria, the severity of the complications at baseline is more important than the baseline BMI in determining the management plan for the patient.³⁵ These staging systems include the EOSS, CMDS, AACE, and KOSC. Of these, the most practical and popular is the EOSS, which classifies the health burden associated with overweight and obesity into 5 stages based on a combination of the patient's medical, mental, and functional disorders.³⁶ The EOSS was proposed as a guide to treatment intensity for weight loss. The CMDS is a guide for treatment of obesity and provides a quantitative assessment for both future diabetes and all-cause and CVD mortality.³⁵ The AACE published

the “Advanced Framework for a New Diagnosis of Obesity as a Chronic Disease” in 2014 which is a guideline whose approach is to determine the intensity of therapy based on disease severity, and treatment goals are defined by sufficient weight loss to prevent and ameliorate complications.³⁷ The KOSC is slightly different from the other staging criteria as it facilitates a holistic evaluation of obese patients. The criteria comprise the following health domains: airways, BMI, cardiovascular disease, diabetes, economic complications, functional limitations, gonadal axis, health status (perceived), and body image.^{23,38} All these staging criteria are useful in evaluating and managing obesity and the choice of which to use may be related to preference of the managing physician.



In the management of obesity, the overall treatment goals are to achieve and maintain a healthy weight, reduce obesity-related complications, and improve the individual's quality of life. The initial approach is to start with lifestyle modification, and its goal is to achieve weight loss through diet modification, increased physical activity and behavioral modification. Although initial rapid weight loss is achievable with reduced caloric intake, long-term weight maintenance remains a challenge.³⁴ The maximum weight loss with lifestyle intervention is usually achieved at 6 months which is followed by a plateau and eventual weight regain over time.³⁹ To achieve long-term weight loss goals, supervised lifestyle intervention is an integral component of obesity treatment strategies. It is essential to have an individualized approach to management with realistic and achievable weight loss goals.

Although lifestyle modification is a crucial component in achieving weight loss, it is very challenging to maintain a healthy lifestyle. It is for this reason that dietary supplements have become very popular adjunctive therapies.⁴⁰ However, there is currently insufficient evidence to recommend the use of herbal medicines for weight loss management.⁴¹

Anti-obesity pharmacotherapy is recommended as an adjunct to lifestyle modification to help increase and maintain weight loss and decrease the risk of obesity-related complications. In addition, long-term pharmacotherapy may be needed to maintain target weight loss and achieve significant improvement in clinical outcomes. International guidelines recommend pharmacotherapy for individuals with BMI ≥ 30 kg/m² or ≥ 27 kg/m² in the presence of cardiometabolic obesity-related risk factors or complications.^{24,34} Australia and Malaysia follow these recommendations, while New Zealand only recommends pharmacotherapy in individuals with a BMI ≥ 30 kg/m².^{26,27,30} However, lower BMI thresholds have been used for the Asian population based on the occurrence of obesity-related complications seen at a lower BMI compared to non-Asian population.³⁴

Guidelines from India and Indonesia recommend initiating medication at BMI ≥ 25 kg/m² if with comorbidities, but, while India endorses pharmacotherapy for all individuals with a BMI ≥ 27 kg/m², Indonesia uses a higher BMI cutoff of ≥ 30 kg/m².^{31,32} South Korean guideline proposes additional pharmacologic treatment for all adults with a BMI ≥ 25 kg/m² after failure of non-pharmacologic methods, and Pakistan further recommends lower BMI thresholds with a BMI ≥ 23 kg/m² with comorbidities or ≥ 25 kg/m².^{29,33} Survey results are generally consistent with local guidelines except in India and Pakistan where the cutoffs are higher. This again may be due to a delay in the application of guideline recommendations in clinical practice.

Based on the 2013 AHA/ACC/TOS guidelines, the recommended initial weight loss goal is 5-10% of baseline weight within 6 months.³⁹ Four drugs, namely, semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate ER and naltrexone-bupropion ER are approved for long-term use and have resulted in significant weight loss with insignificant risks.⁴² Based on a network analysis by Atlas et al⁴³ to compare the efficacy of the Glucagon-Like Peptide-1 (GLP-1) receptor agonists with other anti-obesity medications, semaglutide (13.7%) and liraglutide (9.1%) achieved a greater percentage average weight loss at one year from baseline than phentermine-topiramate (5.0%) and naltrexone-bupropion (4.6%). All medications had greater discontinuation due to adverse events compared to placebo.

In a real-world setting, the use of anti-obesity medications approved for long-term use achieved a maximum % total body weight loss (TBWL) of 10.5% at 24 months based on a retrospective multi-site study by Calderon, et al⁴⁴ where the top 3 prescribed medications were phentermine-topiramate extended-release (ER) (51 %), followed by liraglutide (26.3 %), and bupropion-naltrexone sustained-release (SR) (16.5 %). However, a weight regain of 96% of TBWL was noted after 12 months of discontinuing the medication. The response to treatment was highly varied. Adverse events were common with all medications.

Additional research efforts should focus on improving efficacy and tolerance of anti-obesity medications.

Other medications used to a lesser extent are phentermine and diethylpropione which are approved for the short-term management of obesity (<12 weeks).^{34,44} Metformin, dulaglutide and SGLT-2 inhibitors are approved and primarily used for type 2 diabetes, however, these medications can also promote weight loss. The choice of drug therapy should be individualised based on the patient’s comorbidities, presence of obesity-related complications, efficacy, side effects and cost.

Majority of the investigators from the Asia Pacific countries who participated in this survey have experience in obesity management and use of pharmacotherapy. Their knowledge and experience will be a valuable resource for future clinical trial planning and recruitment.

The availability of different anti-obesity drugs has provided physicians with a wide selection of options to manage their patients. However, side effects are an important consideration when developing a personalized patient treatment plan. This is also an important concern in obesity clinical trials where reduced treatment tolerability is significantly associated with treatment discontinuation, and thus, has a negative impact on patient retention.⁴⁵ Survey results on common side effects experienced by patients are consistent with known side effects of anti-obesity drugs. Due to orlistat’s inhibition of lipases leading to a decrease in intestinal absorption of triglyceride, common side effects include steatorrhea, increased defecation, fecal urgency, and flatus with discharge. Common side effects associated with phentermine-topiramate are insomnia, paresthesia, dizziness, dry mouth, dysgeusia, and constipation. Naltrexone-bupropion’s known side effects include headache, dizziness, dry mouth, and gastrointestinal discomfort (i.e., nausea, vomiting, constipation, or diarrhea). Its effects on BP elevation and heart

Table 1: BMI Cutoffs

COUNTRIES	BMI CUTOFF: SURVEY RESULTS (IN KG/M ²)		BMI CUTOFF: CLINICAL PRACTICE GUIDELINES (IN KG/M ²)	
	Overweight	Obesity	Overweight	Obesity
Australia	≥25	≥30	25.0-29.9	≥30
India	≥25	≥30	≥23	≥25
Indonesia	≥24	≥25	23.0-24.9	≥25
Malaysia	≥23	≥27.5	≥23	≥27.5
New Zealand	≥25	≥30	25.0-29.9	≥30
Pakistan	≥25	≥30	≥23	≥25
Philippines	≥23	≥25	≥23	≥25
South Korea	≥23	≥25	23.0-24.9	≥25
Thailand	≥42	≥32	≥23	≥25
Vietnam	≥23	≥25	≥23	≥25

rate make it challenging to prescribe to patients with significant cardiovascular disease.⁴⁶ GLP-1 receptor agonist drugs, semaglutide and liraglutide, along with dual GLP-1 and GIP receptor agonist, tirzepatide, have gastrointestinal side effects of nausea, vomiting, diarrhea, constipation. Majority of these side effects are transient, occurring in the first 4-20 weeks of starting the medication and are mild-moderate in severity.⁴⁷

A systematic review and meta-analysis of 154 trials (n=112,515),⁴⁸ showed that all these drugs were associated with high rates of discontinuation due to adverse events with tirzepatide presenting the highest risk. GLP-1 receptor agonists were associated with higher risk of gastrointestinal issues, with tirzepatide having the highest risk of vomiting and gastroenteritis. Semaglutide had the highest risk of abdominal pain, while liraglutide had the highest risk of diarrhea. Naltrexone-bupropion had the highest risk of dizziness and increased palpitation, while phentermine-topiramate showed the greatest risk of insomnia.

One reason for the high risk of patient discontinuation and dropout in obesity clinical trials is lack of tolerability of the study drugs due to their side effects. The dropout rate is usually more than 20% but may be significantly higher.⁴⁹ Ways to manage retention concerns due to tolerability issues include allowing for down-titration of the drug dose in patients who are unable to tolerate the assigned dose due to the side effects, and adopting a patient-centric approach by understanding and addressing patients' needs and establishing consistent communication and engagement through proactive education on the trial and the study drug.

In the management of obesity, there is value in health care models that are patient centered. Patients' perceptions, knowledge, and concerns about their disease and ways to manage it play a vital role in the success of treatment. Results of the IMI2 SOPHIA study,⁵⁰ a small study involving authors from Ireland and Kuwait, showed that people with obesity complications identified weight loss outcomes and

effects on their obesity-related complications and quality of life as major influencing factors in their choice of obesity treatment. They also voiced concerns on side effects, availability of support, follow-up, and taking the medication for life. The results of our survey are similar to the findings of this study, though in contrast, our results showed cost of treatment to be the most common issue. This may imply that patients' choice of treatment may be influenced by a drug's reimbursement status in their country. Additionally, patients in the region may be willing to participate in obesity clinical trials as their treatment will be covered in the trial.

Bariatric surgery has become a recognized and effective method for managing severe obesity when non-surgical methods have been unsuccessful. Survey results on the percentage of patients undergoing bariatric surgery are consistent with data from registries in the region, however the data are lower compared to global statistics as reported in the International Federation for Surgery for Obesity and Metabolic Disorders (IFSO) 8th Global Registry Report, 2022.⁵¹ More than 500,000 bariatric surgeries worldwide were reported. Surgical data from Malaysia, South Korea, Australia, and New Zealand were included in the report. Except for Australia which had 20,222 surgeries, the rest of the APAC countries had 2000 or less surgeries. Countries from Europe and the United States reported larger numbers, with the USA having more than 230,000 surgeries. The lesser number of bariatric surgeries performed in the APAC region may be beneficial for obesity clinical trials that will be conducted in the region. As these trials generally exclude patients with a history or plan for bariatric procedure, there may be more patients without any history of bariatric procedure eligible for trial participation.

The survey's two most common reasons for referral for bariatric surgery, morbid obesity and obesity-related complications, are aligned with Asian and global guidelines. The 2022 Joint American Society of Metabolic and Bariatric Surgery (ASMBS) and IFSO guideline for metabolic and bariatric surgery⁵² strongly

recommends bariatric surgery for patients with a BMI ≥ 35 kg/m² regardless of presence or absence of obesity-related complications. It also recommends surgery for patients with BMI < 35 kg/m² who have type 2 diabetes mellitus or other comorbidities or who do not achieve substantial or durable weight loss or comorbidity improvement with nonsurgical methods. This is very similar to many Asian clinical practice guidelines³¹⁻³⁴ though the South Korean guideline²⁹ further recommends that patients with type 2 diabetes mellitus and a lower BMI of ≥ 27.5 kg/m² should be considered for bariatric procedures as well. On the other hand, Malaysia, and Thailand use a higher BMI cutoff of ≥ 37.5 kg/m² regardless of obesity-related complications, and ≥ 32.5 kg/m² for patients with complications.³⁴ Australia and New Zealand likewise have higher BMI cutoffs. Australia uses a BMI cutoff of > 40 kg/m² for patients regardless of complications, while both countries recommend a BMI ≥ 35 kg/m² for patients with obesity-related complications.^{26,27} The Joint World Gastroenterology Organization (WGO) and IFSO guideline for Obesity recommends similar BMI cutoffs for bariatric surgery as Australia and New Zealand.⁵³

their aptitude for conducting clinical trials, all the Investigators were well experienced, had the right infrastructure and patient pool to participate in clinical trials. They acknowledge, however, the presence of common recruitment barriers that can negatively affect recruitment, thus, it is crucial that these are managed. Mitigation plan for these barriers includes review of the eligibility criteria to allow more recruitment, selection of optimal trials sites with the target population focusing on primary care centers and specialty weight loss or obesity clinics, reduction of site visit frequency by allowing home visits and allowing flexible appointment schedules and regular patient engagement to educate them about the trial.

With respect to the investigator landscape and



Conclusion

Obesity is a growing public health concern in the Asia Pacific region, posing significant health and economic challenges. Thus, effective and holistic obesity management is essential.

The diagnosis and management of obesity in the region is aligned with global recommendations and practices. In addition to lifestyle modification, pharmacotherapy is used as an adjunct to achieve and maintain weight loss goals. Improving the efficacy and safety profile of anti-obesity drugs should be the focus of future research and development.

The rising prevalence of obesity in the region, the expertise of investigators in evaluating and managing overweight and obese patients, their experience in the use of anti-obesity drugs, and their clinical trial exposure and interest, make the Asia Pacific region a promising environment for expanding clinical trials in obesity.

Disclosures

Authors Cecilia Sison, Ena Ang, Charu Gautam, and Sujata Routray are employees of IQVIA, a contract research organization that provides scientific and technical services for clinical trials conducted by pharmaceutical companies involved in new drug development. Other than this, all authors declare no professional, academic, competitive, or financial conflicts of interest related to this article. No specific funding was used in the survey and in the preparation of this article.

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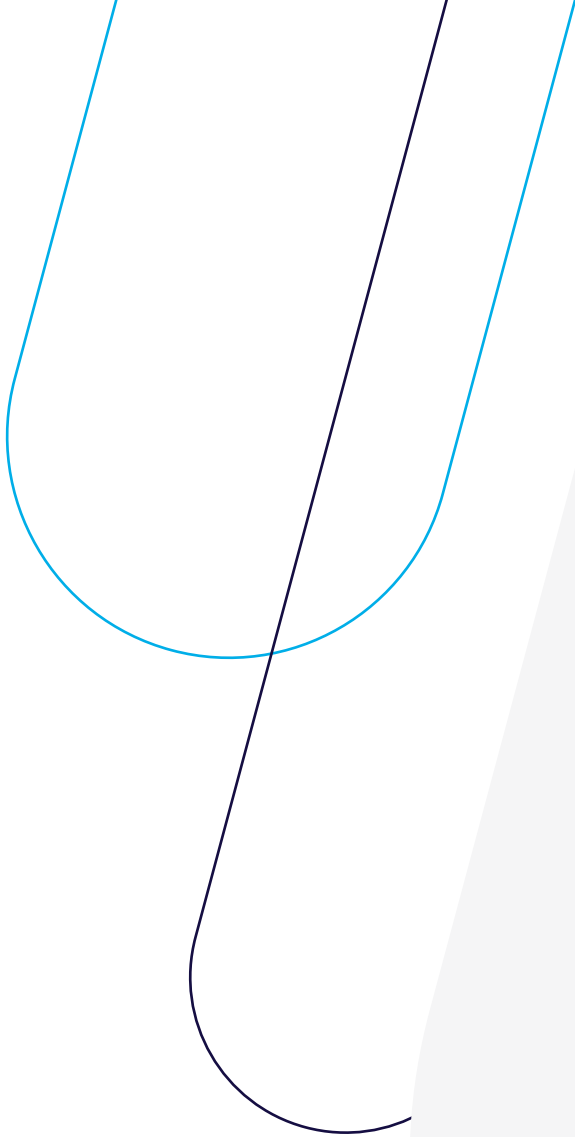
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